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IN THIS issue will be found a group of papers by individuals who have played an important part in extending the surgeon's knowledge of the problems of nutrition in patients with surgical disease. Historically, the surgeon's interest in parenteral fluids was in large measure responsible for much of our recent advances in the science of nutrition. In addition, the significant advances that have been made in the better preparation of the patient for operation, and more adequate support of the patient during and after operation, have added greatly to a reduction in the morbidity and mortality from major surgical procedures. The common factors of anemia, hypoproteinemia, avitaminosis, and other nutritional inadequacies are found to a variable degree in nearly all patients presenting themselves with major surgical lesions, especially of a chronic nature. It is clearly of great importance that every effort be made to correct these deficiencies prior to subjecting the patient to anesthesia and operation.

The surgeon often has no time to waste in getting the patient prepared to a maximum extent possible for such operative procedures as are necessary. For this reason, he resorts to the transfusion of blood and plasma in anemia, and in certain instances of hypoproteinemia. The development of hypoproteinemia is dependent upon many circumstances. It is, in part, due to an inadequate intake of foodstuffs, in part to an extravagant loss of protein in the stool during periods of diarrhea, to impaired digestion and absorption, to impaired protein synthesis, and to increased catabolism. Hypoproteinemia has come to be recognized as a deficiency in a broad sense, and as such it indicates a general depletion of body protein.

There are many reasons why the patient's nutritional status is of prime consideration to the surgeon. The undernourished patient has an increased tendency to develop shock during anesthesia and operation. He has an increased tendency to serious disorders of the liver and to faulty wound healing, and, at times, to an increase in the time necessary for a bolus to pass from the stomach to the rectum. Furthermore, the patient with hypoproteinemia is more susceptible to infection because of a

decrease in antibody formation, and thus one important biological factor in the control of infection is impaired.

Although the clinical signs of vitamin deficiency are frequently absent, it is reasonable to assume that in patients with prolonged illness, and a history of prolonged faulty dietary intake, a subclinical vitamin deficiency must, indeed, exist.

Our recent better understanding of the nutritional problems of our patients has permitted more extensive operative procedures under prolonged periods of anesthesia with the very desirable reduction in the morbidity and mortality from these operative procedures—a goal to which the modern surgeon is devoted. Because the experiences of active workers in the field of nutrition as applied to surgery might be of practical value to all clinicians, a group has been invited to present their current views. It is hoped that this Symposium will add materially to the knowledge of those who read it. The editor wishes to thank all those who have participated in making this special issue of the *American Journal of Clinical Nutrition* possible.

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Principles of Surgical Nutrition

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THE BASIC knowledge of nutrition necessary for the application of a few principles to daily practice is important to every surgeon. Since the surgeon understands the effects of poor nutrition, the correction of either deficits or excesses should not be delegated completely to other personnel. Current literature properly deals with the correction of nutritional deficits through the establishment of positive nitrogen balance and the realization of weight gain.^{1,2,3} On the other hand, the experienced surgeon faced with malnourished patients may find that weight gain is practically impossible to obtain before the necessary operation, particularly in those patients with malignant diseases or pyloric obstruction. He therefore becomes more interested in a few principles as to when and how much blood should be given in preparation of the malnourished patient and when, if ever, blood volume determinations are required.

While experimental and clinical observations have been largely directed toward the correction of problems in the malnourished patient, there has been a tendency to overlook or ignore the more common and equally dangerous factor of obesity, so common in this nation of overweight people. The dangers of obesity to life expectancy, supported by life insurance data, are being publicized in lay magazines; and every surgeon is familiar with the technical difficulties encountered when surgery is required in these patients. Yet all too often the effects of obesity on surgical morbidity are overlooked by both the patient and the surgeon, and the patient is scheduled for operation without due consideration having been given to the excess weight. The surgeon must be weight-conscious every day with re-

spect to every patient, and being familiar with ideal weight as given in standard insurance tables, he must evaluate more closely the patient's actual weight. Familiarity with daily weight trends in hospitalized patients may be just as important as the checking of temperature, pulse, and respiration. It follows, therefore, that the surgeon must be able not only to prepare the malnourished patient for operation but also to assume the moral obligation of refusing elective surgery in the obese patient until weight reduction has been achieved.

OBESITY

Evaluation

Even when the patient is obviously overweight, a more careful evaluation is important. This can be readily achieved without complicated calculation by comparing the present weight with a standard insurance value according to sex and height. Knowing the patient's height and present weight, a simplified method such as that shown in Figure 1

CALCULATION OF IDEAL WEIGHT

1. BASIC WEIGHT FOR 5' FEMALE IS 112*
2. ADD OR SUBTRACT 8* FOR LARGE OR SMALL
3. ADD 8* IF MALE
4. ADD 4* FOR EACH INCH OVER 5'
5. ADD OR SUBTRACT 5* FOR RANGE

EXAMPLE	AVERAGE 5' 8" MALE
BASIC	112
AVERAGE	0
MALE	8
8" x 4*	32
	152 (147* to 157*)

● MINIMUM OPTIMUM WT IS 147*

BASED ON LIFE INS. STATISTICS, METROPOLITAN - SCOTT '51

Figure 1

can be used for a rapid evaluation of the patient's weight. For instance, a 5'8" man of average build who weighs 210 pounds should be considered too obese for elective hernia repair or cholecystectomy. By simple calcula-

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tion he will be found to be 60 pounds overweight. His ideal weight would be 112 pounds plus 8 (male) plus 4×8 (32) or 152 pounds. Even if a plus or minus range of 15 pounds is accepted, he is obviously too obese. While this obesity will be apparent without any calculation, the comparison with ideal weight helps in planning for preoperative weight reduction. Usually this weight may all be due to fatty tissue alone, but mild heart failure or salt retention must also be considered.

Effects

Several complications are more common and less easily prevented in obese patients, particularly in the older age group. Surgeons are familiar with the handicap to accurate diagnosis and the difficult or limited operative exposure which poses increased technical difficulty in the obese patient. Nurses may have made them further aware of the problem of delayed ambulation with its associated increases in ileus, atelectasis, or pneumonia. While it is true that obesity is quite common and many operations are required before weight reduction can be achieved, the high incidence of complications suggests that it is time for more attention to be given to weight reduction before elective surgery is performed if morbidity is to be improved.

Corrective Measures

Since many obese patients feel and appear to the physician to be "in excellent health" there seems little reason to accept the fact that weight reduction is necessary. Often reduction diets have been given but weight loss has not occurred. Most patients can lose weight if adequately impressed with its importance, but few grossly obese individuals will attain their ideal weight. Furthermore, many operative procedures cannot be long delayed. Weight reduction must, therefore, be more strongly urged before purely elective procedures. This can best be achieved by impressing the patient with an anticipated shorter convalescence; and a simplified reducing method must be used.

With simplicity, a graphic chart can be prepared for the patient as a guide to weight re-

duction (Fig 2). With weight on the side and time in days on the bottom of the chart, weight reduction can be easily recorded. From the present weight a line is drawn to represent the recommended weight reduction over a specific period. The patient then plots a daily weight course which, when above the expected line, signifies that less must be eaten.

Diet instructions must also be as simple as possible. Charts are available for the patient which show not only the caloric value of commonly eaten foods, but also those for many snack foods and beverages. The patient, instructed to follow and keep record of a 1200 calorie diet, may find originally that he has eaten the majority of the day's allowance by noon; however, the calorie intake will gradually be more easily spread throughout the day. Some patients may prefer to omit one meal in preference to another, or to defer most of lunch for a larger dinner. Other patients cannot accept the decreased intake of 1200 calories because of the low bulk; for them some groceries and special food stores carry numerous appetizing low caloric foods, such as preserves made without sugar, salads made without oil yet which seem oily, and so forth. Supplemental vitamins are not usually required with such a reduction plan. Drugs used to reduce may give the patient a false sense of security since weight loss is still dependent entirely upon decreased intake through loss of appetite.

Only a reasonable weight reduction should be expected.⁴ A scale of weight loss based on the weight at the time reduction is begun may serve as a guide to the physician. It should show that a 150-pound obese patient can lose only about 10 pounds. An additional 5-pound loss can be anticipated for each 25 pounds in excess of 150 pounds. For instance, if the beginning weight is approximately 175 pounds, 15 pounds weight loss should be expected, and if the original weight exceeds 250 pounds, a 35-pound loss should be expected. If, after this weight reduction is approximated, further loss seems improbable, operation should be considered, particularly if further delay will predispose to complications of the disease for which the operation is required.

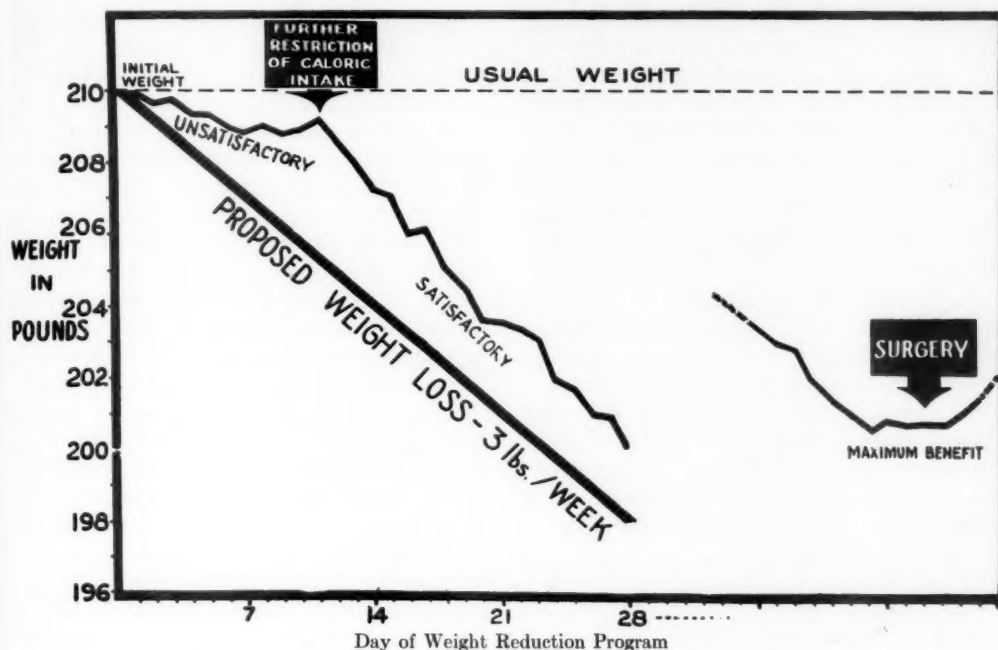


Figure 2. The personal weight chart, a guide to the physician—a daily reminder to the patient.

WEIGHT LOSS AND MALNUTRITION

Evaluation

Most important in the appraisal of nutritional deficits is an appreciation of what constitutes *malnutrition*. While severely debilitated patients are uncommonly seen, except in the larger medical centers to which they may be referred, moderate weight loss as the result of cancer or another chronic disease is commonly encountered in every surgical practice. Physicians in the past have been prone to accept such weight loss as a normal result of disease, yet blood volume and available protein stores are almost invariably depleted when there is an involuntary weight loss. These patients may appear in apparent good preoperative condition unless a correct appraisal is made.

Preoperative evaluation of these patients requires a correlation of the history, physical findings, and a correct interpretation of a few carefully selected laboratory studies. Actual

weight loss may be masked by edema. Acute weight loss or the presence of exudative or transudative lesions such as gastric or right colon carcinoma increase the loss of both red blood cells and protein. This is particularly true of the blood total protein determination which alone is not an accurate measure of total circulating available protein, so important in wound healing. Therefore, the estimation of blood volume deficits which simultaneously occur with weight loss and chronic illnesses is of great value. However, the actual volume determination in all surgical patients is neither mandatory nor more than supplemental to sound clinical judgment.

Although protein and blood volume changes vary somewhat with the nature of the disease, they are primarily related to weight loss. Deficits have been found to range between 50 and 100 ml of whole blood per pound of weight lost.⁵ The lower value usually is applicable to the uncomplicated cases of jaundice or gastrointestinal cancer. The higher

value is less commonly encountered and applies to those patients with such problems as intestinal fistulae or chronic ulcerative colitis. Obviously, a history of gastrointestinal bleeding must be considered with weight loss. Less often appreciated is the severe blood volume depletion found in those patients with chronic weight loss who suddenly increase their protein losses from a complication such as acute intestinal obstruction.

In an occasional complicated or poor risk patient, actual blood volume determinations will be required. The methods, utilizing either Evans blue dye or radioactive iodinated human serum albumin, have been described and are relatively simple.^{6,7} Such an accurate evaluation is most important in intestinal fistula and in the elderly poor risk patients with severe weight loss, particularly when there is an associated heart disease.

Effects

Most of the effects of malnutrition are generally appreciated. Anemia and hypoproteinemia are common. Unless red blood cell and protein volumes are adequately replenished there is an increased tendency to surgical shock.⁸ Severe malnutrition may be associated with liver injury which further contributes to lowered protein stores and to a decreased tolerance to anesthesia. Poor wound healing, edema of gastrointestinal suture lines, and frequent disturbances in intestinal mobility,^{9,10,11} may lead to subsequent complications such as peritonitis from a suture line leakage or atelectasis from abdominal distention. Prevention of these complications demands that every effort be made to correct nutritional deficits, if possible, before the patient is operated upon.

Corrective Measures

Two facts must be accepted as prerequisite to the practical management of nutritional deficits. First, the urgency of surgical intervention or the location of the disease itself in many patients usually prevents weight gain through adequate caloric intake. While blood transfusion is important, its value is not in calories. Second, nutritional improvement will

not be achieved unless close personal attention is given to the patient. Every effort must be made to apply correctly all the methods available for feeding these patients.

In those patients in whom neither oral, gastric tube, nor intravenous feedings are to be given for long preoperative periods, blood volume replacement assumes priority. Despite the obstacles in nutritional therapy, these malnourished patients will tolerate operations well if blood volume deficits are corrected. The blood volume replacement must be guided by a correct evaluation of deficits. Too rapid replacement may be dangerous in elderly individuals,¹² and several days will be required to replace the 1000- to 1500-ml-volume deficits in some patients. During this period ambulation and as much oral intake as practical should be encouraged. The surgeon often accepts that some body tissue breakdown continues, but this can be partially prevented even with a relatively low caloric and protein intake. Excessively vigorous efforts to achieve high caloric and protein intakes often either delay the operation or result in a set-back from vomiting or diarrhea.

Maintenance of nutrition and the correction of deficits require both a basic knowledge of common foods and food supplements and a willingness on the part of the surgeon to evaluate and, if necessary, change his plan of management. Too often a high caloric and high protein diet is ordered for a patient with no teeth, no appetite, and a distinct dislike for milk or some other basic food element; yet the surgeon may wonder why the patient's status remains unimproved. While frequent weight recordings are important, an increase due first to restoration of water balance and later to edema may be misinterpreted unless actual food intake is recorded. This recording of food intake can be performed by the dietitian and made a part of the patient's hospital chart; however, adequate dietary help is not available in most hospitals. It therefore becomes the responsibility of the surgeon to be sure that the prescribed foods are eaten or that, when necessary, the diet is supplemented with either tube feedings or intravenous therapy. This requires visits to the patient's bed-

side at mealtimes to assess the intake of food.

The application of practical knowledge of the caloric and protein values of common staple foods is often all that is required. Milk, meat, bread, potatoes, and eggs are common foods eaten. When one of these is not acceptable, adequate nutrition may be obtained with another. A rapid assessment of what has been eaten tells the surgeon how much protein and calories have been consumed. Milk contains approximately 160 calories and 8 grams of protein per glass. Supplemented with vitamins and iron, this forms a very satisfactory material for total feeding; but only a few patients will accept orally three quarts of milk a day! An egg contains approximately 6 grams of protein and 80 calories; one serving of meat, 300 calories and 18 grams of protein; two slices of bread, 3 grams of protein and 130 calories. If a simplified formula establishes daily requirements to be 1 gram of protein and 20 to 25 calories per pound of body weight (approximately twice the National Research Council's values for normal man) the practical significance of a knowledge of the values of these common foods is appreciated. If, after evaluating the patient's likes and dislikes and ordering a proper diet, the patient fails to gain, then supplemental feedings will be required.

Tube feedings may be required for all nutrition or to supplement oral intake. When the latter purpose is served, feedings should be so spaced as not to curtail the appetite. When it appears certain that adequate oral intake can again be achieved, the tube may be removed. For the patient's comfort, a small polyethylene or polyvinyl plastic tube of about 5 mm diameter is preferable to the commonly used Levine tube. The feeding mixture should be a simple, easily prepared and well-tolerated one; and recognition should be given the fact that rich protein and high caloric feedings are rarely tolerated by the malnourished patient.

Homogenized milk is one of the best feeding materials and is readily available, requiring no special preparation.¹³ Adequate maintenance can be obtained on three quarts a day; and when vitamins and iron are added, this is probably one of the most practical tube feed-

ings for the average hospital. When more calories and protein are required, skim milk powder may be added. Several protein and carbohydrate mixtures have been prepared commercially, most of which are low in sodium and contain both carbohydrate and the essential amino acids. When given in too concentrated form, nausea, vomiting, and diarrhea may result. From a practical standpoint, homogenized milk is readily ordered and easily given by lay personnel, or taken by the patient himself. Furthermore, homogenized milk can also be used for either gastrostomy or jejunostomy feedings, which means that complicated formulas are not required no matter what the method of supplemental alimentary feeding.

Gastrostomy or jejunostomy becomes necessary when either high gastrointestinal obstruction is present or prolonged feeding is anticipated. Gastrostomy is more satisfactory from a feeding standpoint, but may be contraindicated if further operations on the stomach or esophagus are planned. The semipermanent gastrostomy advocated by Patton¹⁴ is quite satisfactory, and the feeding tube can be inserted at intervals by the patients. As an alternative, a simple Stamm type jejunostomy using a No. 16 or 18 mushroom catheter is easily performed. While homogenized milk will again serve as an excellent tube feeding, the volume should be kept very low, and only gradually increased during the first few days; otherwise diarrhea, particularly with jejunostomy feedings, may lead to more rapid weight loss rather than gain. In most cases the patient with a jejunostomy will be supplemented for the first few days with intravenous therapy.

Disagreement regarding optimal caloric requirements necessary to reach nitrogen balance by the intravenous method is largely due to a failure to consider whether protein maintenance or restoration is either desired or attainable. As little as 6 calories per kg of body weight will minimize further protein tissue breakdown at the expense of some body fat.¹⁵ This can be supplied with 2 liters of 5 per cent dextrose in 5 per cent protein hydrolysate daily. Protein restoration and weight gain require 30 to 45 calories per kg. This is

rarely if ever attained for long periods of time. From a practical standpoint, the more complicated intravenous fluids have only special applications.

While positive nitrogen balance can be achieved in the undernourished patient with as little as 100 grams of hydrolyzed protein and 400 calories by glucose,^{2,15} the simultaneous importance of fluid and electrolyte balance and several other factors must be considered. As a rule, 10 per cent glucose solution should be given preference over the routine ordering of 5 per cent intravenous solutions. The increased cost for double the number of calories is minimal. Fructose-containing solutions have stirred great comment, but the small and even questionable benefits derived seem hardly worth the increased cost.¹⁶ Alcohol-containing solutions are of greatest practical value when sedation as well as calories are desired. While as much as 1 calorie per ml has been given by the intravenous route,¹⁷ long-term therapy will probably remain inadequate until a stable, safe fat emulsion is available.

ANCILLARY SUPPLEMENTS AND VITAMINS

Supplementary vitamins and special ancillary methods helpful in improving intake, absorption, or utilization are important. Small doses of testosterone to produce positive nitrogen balance, or corticotropin (ACTH) or cortisone to increase appetite are probably not considered often enough. Unless there is a contraindication to their use, they may help to attain an adequate caloric intake. Usually they are not indicated prior to a surgical procedure. Pancreatin or emulsifying agents such as Tween 80® will be helpful in those patients with diseases of the pancreas or liver with decreased fat absorption. Vitamins, on the other hand, are often given in great excess, particularly in the well-nourished patient who undergoes elective surgery with an anticipated short recovery. While approximately five times the normal daily requirements of ascorbic acid and the B-complex vitamins are required for the malnourished patient, these amounts are usually present in one commercial ampule. The giving of several such ampules

daily serves no purpose other than to increase hospital expense.

SUMMARY

The numerous advances in nutrition made through clinical and laboratory studies should serve as a guide to practical nutritional therapy. A basic knowledge of nutrition is important but serves little purpose if careful attention is not given to actual diet intake and weight trend. Day-to-day evaluation of weight should be as routine as the evaluation of temperature, pulse, and respiration. While emphasis has properly been placed on the problems of malnutrition, there has been a tendency to overlook the equally important factor of obesity.

Morbidity and mortality can be further lowered through the correction of obesity prior to surgery. Whereas weight reduction may not be practical prior to many operations, the time has come for surgeons to refuse strictly elective surgery until some weight reduction has been accomplished. This may best be realized through a simple diet with the evaluation of excessive eating being made and charted by the patient. The anticipation of earlier convalescence should encourage the patient to accept the necessity of weight reduction.

Correction of nutritional deficits can properly be made only through frequent evaluations of the patient's response and a plan of therapy which permits lability in the utilization of several available methods of feeding. Oral intake is preferred and most patients will receive adequate basic requirements if encouraged through changes of diet and supplemental feedings. The application of a knowledge of the protein and calorie values of common staple foods is necessary to the attainment of daily requirements. When oral methods fail, tube or intravenous feedings should be instituted. Homogenized milk offers a practical, nutritious, and readily available source for both gastric and jejunal feedings.

Since many patients with a malignancy or chronic disease cannot await weight gain before operation, the blood volume deficits in these patients must be appreciated. Blood

volume deficits are somewhat related to weight loss; a 50-to 100-ml deficit per pound of lost weight has been found. Despite weight loss, these patients will tolerate surgical procedures, if blood volume deficits are corrected.

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Nutritional Evaluation during the Altered Physiological State after Injury

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THE RESPONSE to severe injury appears to be a response of every system, every organ, and presumably every cell in the body. It is a response, not of the moment, but of days or weeks. The magnitude and duration of this response appear to be directly proportional to the magnitude of the injury.

Since this response is primarily metabolic in nature, it is not surprising that almost every metabolic study reveals a deviation from the normal pre-injury state.

Most injuries include at least three components—the destruction of tissue, the loss of blood, and a break in the defense against bacteria. Each component of injury evokes additional facets of the metabolic response. For example, the loss of blood is associated not only with the inherent loss of its substances but with the changes brought on by renal vasoconstriction, by the autonomic response, by the adrenal cortical response, and by the increased production of red blood cells, albumin, fibrinogen, platelets, and other components. The destruction of tissue may be associated with the loss of water or plasma as local edema and with the increased metabolism of the cellular proliferation of wound healing. Infection increases the exudate, increases the destruction of tissue, and evokes leukocytic and antibody responses.

The above changes are used only as examples of the complex nature of injury and the responses which are evoked. Without an appreciation of this dynamic state, the physician may discover many pitfalls in his evaluation of the nutritional state of the postoperative or post-injury patient.

POTASSIUM AND NITROGEN

Associated with tissue destruction there is an increased excretion of potassium and nitrogen in the urine. This appears to be due not only to the adrenal cortical response but also to the increased destruction of tissue (Fig. 1). A patient with an acute arterial injury and a resultant gangrenous limb may excrete far more potassium and nitrogen than does the patient with an amputation stump free of necrotic tissue.¹ This increased metabolic load coincides with a period of renal vasoconstriction and decreased glomerular filtration² so that in the absence of pre-existing renal disease, a relative retention of nitrogen or potassium may occur and be associated with rising plasma concentrations. A transient rise in the concentration of potassium in the plasma is not uncommon on the day of severe injury. Unless renal damage is severe, the plasma potassium concentration rapidly returns to a normal level.

Even though the plasma potassium concentration returns to normal, the blood urea nitrogen concentration may continue to rise for several days, although the total nitrogen excreted in the urine remains elevated (Fig. 2). These findings, after very severe injury, do not suggest the presence of pre-existing renal disease, but if noted after minor trauma, strongly suggest the presence of a pre-existing impairment of the renal reserve.

SODIUM

Coincident with the potassium and nitrogen diuresis, there is a conservation of sodium and water. The net conservation of sodium over a period of two weeks may amount to 500–900 milliequivalents. In spite of sodium retention, the plasma sodium concentration often falls sharply within a period of a few hours, and may remain at subnormal levels

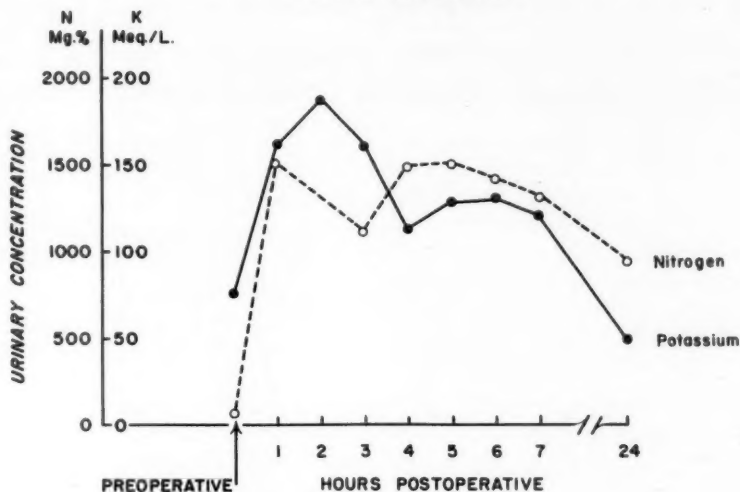
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for several days.¹ Accompanying the fall in sodium concentration, there may be a transient decrease in the total calcium concentration in the plasma.³

taken for diabetes. Similarly, the diabetic patient undergoing operation may have a rise in his blood sugar concentration and may increase his insulin requirements during the

NITROGEN AND POTASSIUM EXCRETION AFTER OPERATION



Nitrogen Balance

Preoperative (24 hours) +1.5 grams

Postoperative (24 hours) -19.7 grams

Potassium Balance

Preoperative (24 hours) +3.2 Meq.

Postoperative (24 hours) -174.9 Meq.

Figure 1

The tremendous mobilization of nitrogen and potassium by a patient who developed a gangrenous extremity as a result of an arterial embolus and unsuccessful embolectomy is indicated.

GLUCOSE

The blood glucose concentration rises with injury as a result of the responses of the sympathetic nervous system and the adrenal cortex. The fasting blood sugar may remain high throughout the week after injury, slowly subsiding toward the normal level. During this time the glucose tolerance curve is "diabetic" in type.⁴ The stress response, being antagonistic to the effect of insulin, is associated with a decreased sensitivity to insulin. Because of the high blood sugar concentration, the normal response to trauma may be mis-

stress response. As a possibly related phenomenon, the serum amylase concentration often falls after nonspecific trauma.⁵

The rise in the blood sugar concentration during acute pancreatitis has often been attributed to an insulin insufficiency. A transient diabetic state due to the destruction of the islet cells is probably quite infrequent. Instead, the elevated fasting blood sugar level, the glucosuria, and the transient diabetic-type glucose tolerance curve are probably nonspecific indications of the severe trauma of acute pancreatitis.

PROTEIN

Although the changes in carbohydrate metabolism may be most marked immediately after injury, the changes in protein metabolism become increasingly evident during the ensuing days. Not only is the nitrogen excretion increased, but the concentration of the

but probably also reflect the continuing nature of the injury—that is, the continuing loss of albumin. Thus the low albumin-globulin ratio after injury does not necessarily reflect a pre-existing state of malnutrition.

A second aspect of the changes in protein metabolism is reflected in the excretion of

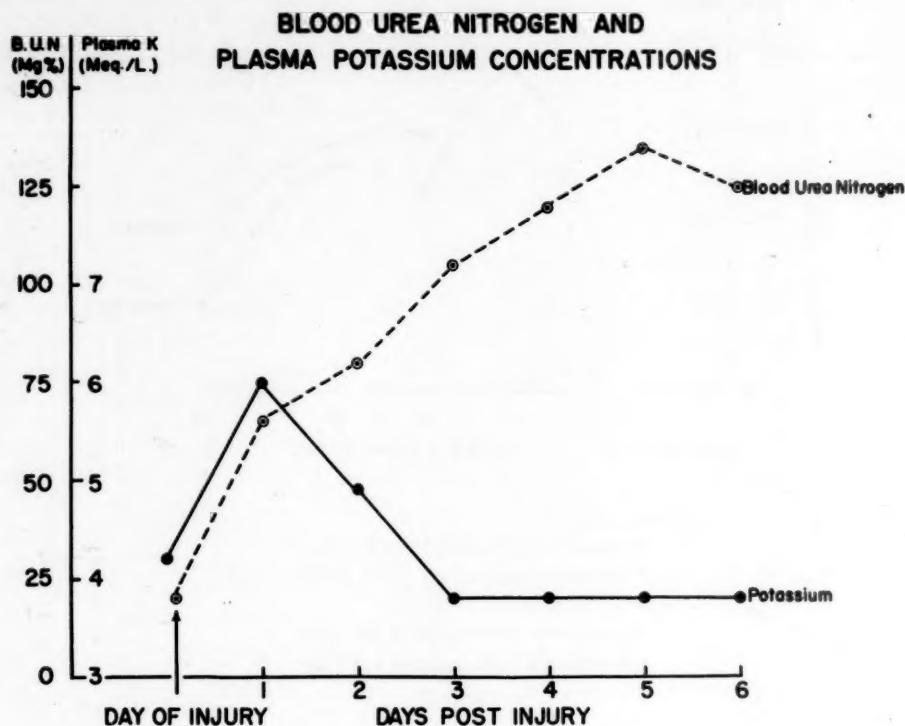


Figure 2

This figure demonstrates the transient rise in the plasma potassium concentration and the prolonged rise in the blood urea nitrogen concentration in a non-oliguric battle casualty.

serum proteins changes in a predictable manner. Following abdominal trauma, there is a rapid, progressive decrease in the albumin-globulin ratio, the ratio often falling to less than one by the third day post-injury. Following injuries of the extremities, the changes are less marked but are qualitatively similar.⁶ Electrophoretic studies indicate a decrease in the relative proportion of albumin and an increase in the α_1 and α_2 globulin fractions.⁶ These progressive changes reflect not only the continuing response of the patient

creatinine and creatine after injury. Severe trauma to any part of the body may result in a sharp rise in the total urinary excretion of creatinine, an excretion which may reach a level of 4.0 to 6.0 grams per day. Similarly, the excretion of creatine may reach a level of 3.0 to 4.0 grams per day, but appears to follow injuries which involve the destruction of large masses of muscle. The latter observation, therefore, has been made in patients with injuries to the extremities in contradistinction to injuries of the viscera.⁷

OTHER CHANGES

Payne and Krauel,⁸ studying one component of lipid metabolism demonstrated further alterations in the metabolism of this component after injury. Studying the lymph before and after thermal injury, they found that the marked increase in lymph flow from the injured extremity was associated with a striking increase in the local mobilization of cholesterol, neutral fats, and phospholipids.

The metabolic response is demonstrated not only by these broad patterns but also in the response of the individual organs and systems.

As a response to combat injury, including hemorrhage, Scott and Crosby⁹ demonstrated a decrease in the clotting time and a rise in the platelet count and fibrinogen concentration. Immediately after injury and resuscitation, the prothrombin activity fell to approximately 50 per cent of normal. This defect corrected itself within one to three days but was followed shortly by a second fall of similar magnitude. Recovery to normal then gradually progressed. This defect could not be prevented by the administration of vitamin K. Rather than being a pure deficiency of prothrombin, it appeared to be a deficiency in the activity of the accelerator globulins. This decreased prothrombin activity after injury is not indicative of pre-existing hepatic disease.

It is well known that hemorrhage is followed within a few hours by hemodilution. Patients who have had a mass of muscle destroyed can have their hematocrit and blood volume maintained by transfusion, but shortly after the transfusion is completed the hematocrit will begin to fall, often resulting in a rather marked anemia as the red blood cells are lost.¹⁰ Conversely, patients with severe abdominal injuries, like patients with severe thermal injuries, lose more plasma than red cells in the postoperative period, often demonstrating an increase in the hematocrit after transfusion has been discontinued.

Injury is followed by a transient decrease in the mean corpuscular volume.¹¹ The significance of this observation is unknown but the finding suggests that these cells lose water to the extracellular compartment, a shift which, if it occurred from all the cells in the

body, might explain the concurrent fall in plasma sodium concentration. Reticulocytosis reflects the bone marrow's response to hemorrhage; the reticulocyte count was 3 to 5 per cent in one study of the severely injured.¹¹

Following severe trauma, the leukocytic response is often quite striking; a count of 20,000 to 50,000 cells per cubic milliliter was often found in the combat casualty a few hours after injury.¹¹ The count often demonstrated a moderate drop while the patient was under anesthesia and undergoing operation. Thereafter, it again rose. Occasionally there would be a precipitous drop in the white cell count to 500-1000 cells per cubic milliliter, a reaction associated with a fall in the platelet count, a fall in the blood pressure, and sometimes a demonstrable bacteremia. This response, the hemoclastic reaction, denotes a rather grave prognosis. The eosinopenia after trauma is so well known as to need no comment.

LIVER FUNCTION

As a result of hepatic ischemia and of the hemolysis occurring after transfusion and in hematomas, a rise in the serum bilirubin follows severe injury and rapid transfusion.^{12,13} On the day of injury and resuscitation, the serum bilirubin may rise steadily to a level of 2.0-5.0 mg per 100 ml, reaching its maximum about six hours after operation and then characteristically subsiding rapidly. This increment is predominantly in the indirect, protein-bound fraction.

Other hepatic function studies may lead to false interpretation unless the response to injury is appreciated. The cephalin flocculation reaction is increased following injury.¹² The magnitude and duration of this change, as with so many of the above changes, appears proportional to the magnitude of the original injury. The thymol turbidity test does not demonstrate an abnormal reaction after injury. These two tests, usually employed to demonstrate disease of the hepatic cells, appear to be based fundamentally on an undefined relationship of the albumin-globulin fractions. The above response in the cephalin flocculation test may not reflect hepatic injury but instead may reflect the acute extrahepatic shifts in the albumin and globulin fractions.

Bromsulfalein retention can almost invariably be demonstrated after severe injury.^{12,13} A retention of 15 to 40 per cent 45 minutes after the intravenous injection of 5 milligrams of bromsulfalein per kilogram of body weight has been described on the day following severe trauma, an observation more frequently found after abdominal trauma than after injury to the extremities. During the week after injury, the excretion of bromsulfalein gradually returns toward normal.

The pitfalls in interpreting prothrombin activity as a test of hepatic function after trauma have been discussed previously.

Studies of the gastrointestinal system have demonstrated a transient achlorhydria after trauma,¹⁴ the frequent failure of roentgenographic visualization of the gallbladder,¹⁵ and a decreased gastrointestinal absorption of water.¹⁶ Renal function studies demonstrate the frequency of albuminuria,¹³ the decreased renal clearance,² and the above-mentioned rise in the concentration of nonprotein nitrogen products in the blood. The adrenal cortical response, the basis for some of the previously mentioned observations, is well recognized.

These are all part of the body's response to severe trauma. They do not represent pre-existing disease or detectable post-injury complication. To fail to recognize the body's total response to trauma will subject the clinician to many pitfalls in the evaluation of the patient in the post-injury state.

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Nutrition and Wound Healing

By PAUL MECRAY, JR., M.D., M.S.C.*

EVERY STUDENT of biology has been fascinated by the regeneration of the severed limb seen in many of the lower organisms. Wound healing is a similar epimorphic process. The chemistry of the process in man is comparatively unknown. At the present time it is necessary to proceed on the premises that what is good for growth is also good for repair, and that experimental data compiled on the dog, the rat, the salamander, and even the axolotl are pertinent in man.

THE HEALING PROCESS

The ideally coapted wound contains a minimum of devitalized tissue to be autolyzed. The wound surfaces are separated by a homogeneous mass of fibrin which rapidly develops into strands. At this time the wound has practically no strength save that inherent in the sutures utilized to close it. After a lag period, fibroblasts derived from the wandering connective tissue cells start their amoeboid motion along the fibrin strands, elongating as they grow out. They are followed by the endothelial buds. The stimulus to this process is not known. Oxygen lack and local nutritional deficiency are possibilities to be considered. Others have suggested that specific chemical substances such as glutathione¹ or its sulfhydryl radical² might be responsible. As the process proceeds with the migration and proliferation of fibroblasts and capillaries, the formation of collagen is evident as the intercellular matrix matures. At this time the strength of the wound increases. Epithelialization is a quite different problem, though an analogous one.

In man, normal wound repair is dependent upon numerous *local factors*. Since even the sharpest scalpel kills some cells, the amount of

devitalized tissue between the coapted edges is important. The amount and character of foreign bodies such as ligatures and bacteria must be considered. The vascularity of the tissues to be repaired and the accuracy of the coaptation of the wound edges without undue separation by blood clots are important factors. It was shown in 1922 by Ebeling³ that a 10 per cent rise in the temperature of a cold-blooded animal would double the rate of wound healing. This indicates that wound healing is a chemical reaction. Thus, if the local factors discussed previously are kept at an optimum, the most important variable is the supply of the components for the chemical reaction. To accomplish this in the human being nutrition must be adequate.

The catabolic effect of trauma and surgical operations have been pointed out elsewhere in this symposium. So far as these effects apply to wound healing we are able to assess only a few of them at this time.

HYPOPROTEINEMIA

The experiments of Clark⁴ in 1919 showed that animals on a high protein diet had a reduced lag period in the healing of surface wounds, compared to those on a high fat, low protein diet. Meeray, Barden, and Ravdin⁵ in 1935 reported that during the course of experiments on hypoproteinemia, the wounds in dogs' abdomens healed poorly while the animals were in the hypoproteinemic state. This Thompson, Ravdin, and Frank⁶ showed to be due to delayed fibroplasia and to the separation of wounds by edema fluid. When the proteins were restored, the wound healed promptly. From this experiment it may be assumed that the delay in fibroplasia was due to edema separating the wound edges or to a lack of available amino acids for repair, or both. There have been numerous other experiments that tend to show that the lag

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period in wound healing is lengthened by hypoproteinemia.⁷⁻⁹ Yet which is the more significant: the edema or the lack of amino acid building blocks? Any surgeon who has operated upon the edematous postmastectomy arm of a patient in good nutritional balance will feel that edema is the more important. Yet it would seem that other local factors are also involved. No satisfactory experiment to clarify this important clinical point has been recorded.¹⁰

The fact that protein synthesis cannot occur if the requisite amino acids are not present at the same time has been well demonstrated.^{11,12} Localio and co-workers¹³ showed in their experiment and in two clinical cases that the addition of *dl*-methionine increased the rate of wound healing. Other authors have felt that amino acids containing the —SH radical were important systemically.¹⁴ The local application of compounds containing the —SH radical in granulating wounds has been discontinued, despite early favorable reports.¹⁵

In man there have been few studies of the pH of wounds such as have been done in the lower organisms, in which marked variations in pH from the regressive phase to the regenerative phase were noted. Such studies might have clinical importance, since animals on an acid diet have been shown to have a shortened course of wound healing.¹⁶ Similarly, there have been no studies on the sulfur/nitrogen ratio which might give a clue to the amino acids locally involved in the lag period and in the healing process.

It is difficult to understand why, in a wide variety of experiments on animals from salamanders¹⁷ to rats,¹⁸ the fasted (but not starved) animal heals at a normal or even accelerated rate. In the early stages of wound regeneration both experimental animals and man seem to be without appetite. It has been suggested¹⁹ that fasting increases the alkaline phosphatase which is known to be in high concentration in healing bone in man and in some healing wounds in lower animals.²⁰ However, few experiments on the alkaline phosphatase content of healing wounds in man have been reported.²¹

CLINICAL IMPORTANCE OF HYPOPROTEINEMIA IN WOUND HEALING

In clinical practice so wide a variety of factors is involved in healing a wound such as an abdominal incision or an intestinal anastomosis that it is an insurmountable task to separate the importance of each factor. Surgeons have for years observed that their malnourished patients produce a great proportion of the wound complications. Yet, without apparent reason, an occasional cachectic patient on whom some emergency procedure is necessarily performed will heal his anastomosis and incision without incident.

One of the few clinical studies on this subject has been done by Localio.²² He determined serum and tissue protein concentrations in patients judged clinically to be normal, to be debilitated, and in those with wound disruption. It appeared from this study that the protein concentration in fascia was of greater import than the concentration of protein in the serum. Examples were shown with normal serum protein concentration in the face of significant depletion of the tissue protein. Among the suggestions offered to account for this is the possibility that tissue protein stores are depleted in an attempt to maintain homeostasis of the serum protein.

The healing of decubitus ulcers with high protein therapy administered to hypoproteinemic patients has remained a clinical landmark.²³ Yet Co Tui points out that decubiti are not commonly found in association with nephrosis.²⁴ Other writers²⁵ have observed depleted serum protein in cases of abdominal wound disruption, yet this cannot be accepted other than as a possible cause of disruption. The degree of the patient's hydration is a factor that can produce wide variation in this determination. This may account for the normal findings in many cases in the reported series. The writer has been impressed with the frequency of the association of wound infection in wound disruption. Cannon²⁶ stresses that the hypoproteinemic animal is also more susceptible to infection.

Levenson and associates¹⁰ have presented numerous cases of healing burns in humans

with a marked delay in healing being manifested in the hypoproteinemic patient. They report some skin graft "takes" actually breaking down as the patients became deficient in protein. Yet every surgeon has had the experience of having skin grafts take perfectly in his patients with huge oozing areas from which protein is being lost more rapidly than it can be replaced by any route; while later, when the patient is in good nutritional balance, the last few grafts necessary to complete the repair may fail.

VITAMIN DEFICIENCY

The fat-soluble vitamins have not been given any assigned role in wound healing in man. It must be presumed that they have a role in the healing of bone wounds, much as they do in bone growth.²⁷ In general, it appears that large doses of either vitamins A or D inhibit the healing of soft wounds in experimental animals. There is conflict as to whether small dosages are helpful. Bush and Lam²⁸ feel that vitamin A will hasten the healing in vitamin A-deficient animals.

The use of vitamin A and D ointments in the clinical care of surface wounds was formerly felt by many workers to promote healing.²⁹ These substances, however, are rarely used today.

The B-complex group of vitamins must be essential to wound healing, according to Needham.³⁰ He points out that they are coenzymes in the transfer of most of the biochemically important simple organic radicals. Bosse and Axelrod³¹ have shown that pyridoxine- and riboflavin-deficient rats show impairment in the rate and quality of wound healing. Biotin deficiency produced less marked changes. Findley³² presents suggestive evidence that vitamin B₁₂ helps increase the strength of wounds in rats during the early healing period.

Vitamin C, ascorbic acid, has been the subject of considerable work in both animals and clinical experiments. Needham quotes a Russian writer (D. D. Ryvkina) as showing that the vitamin C content of a regenerating axolotl limb is higher than normal throughout the repair phase. Other writers likewise have

shown that ascorbic acid is increased at the site of wounding.³³ There seems to be agreement among investigators that vitamin C is necessary for the maturation of collagen and adequate capillary invasion of healing wounds.^{34,35} From a clinical point of view, however, the mode of action is not clear.³⁶

There have been clinical reports of low ascorbic acid levels almost routinely found in patients with wound disruption.³⁷ A considerable number of writers have reported very low serum ascorbic acid levels in patients admitted to general hospitals for surgical operations.³⁸ After a period of hospitalization and preparation for operation, the serum levels of some patients drop even lower. In a careful experiment Wolfer and co-workers³⁹ showed that in human subjects with prolonged ascorbic acid depletion one might expect a 50 per cent diminution in the tensile strength of the wound. The high incidence of wound infection suggested the need for ascorbic acid in the tissues for maximum resistance to infection. Crandon, Lund, and Dill⁴⁰ performed an experiment in which in a man on an ascorbic acid-free diet the serum level dropped to zero in 41 days. Yet about this time an inflicted wound healed satisfactorily. After 82 days the ascorbic acid level of the packed leukocytes had dropped to zero. At 182 days an incision made in the obviously scorbutic individual failed to heal. These writers emphasize the fact that the serum ascorbic acid levels are of less value than those of the packed leukocytes. A similar interpretation might be made from the work of Carney,⁴¹ who observed no difference in the healing of war wounds of soldiers in the Italian campaign on vitamin C-deficient diets and low serum levels, compared to those on adequate diets and high serum levels. On the other hand, most surgeons have the feeling that wound healing is impaired proportionately to the degree of ascorbic acid deficiency.⁴² With the availability of excellent modern multivitamin preparations for oral and intravenous use, it is probable that deficiencies in the vitamin B and C group in postoperative patients are now uncommon. There are no clinical reports on wound healing and disruption in

patients alternately treated with large vitamin doses presently in vogue, compared to controls to whom no additional vitamins were administered.

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Our Forefathers' Blood

"The association of blood with life itself is among the primitive concepts of man. In the picturesque phraseology of the Old Testament, blood is a synonym for vitality, emotion and heritage. It constitutes the basis of one of the plagues described in Exodus when Moses caused all the rivers and streams of Egypt to run red. It is not surprising that both Pliny and Celsus describe the patricians rushing from their seats in the Coliseum down into the arena to drink the freshly flowing blood of dying gladiators.

"The thought that all these vital properties could be transmitted by the act of transfusion is of ancient origin. A rational approach to this act, however, necessarily awaited a clear understanding of the nature of the circulation."

—L. Blum and W. N. Nelson. *Bulletin of the New York Academy of Medicine* 31: 671, 1955.

Social Vomiting

"Long before the advent of any tube the simplest procedure by which to expel the gastric contents was to place a finger in back of the tongue to stimulate the vomiting reflex. Because such an act was crude the rulers of Rome who feasted for days introduced a vomiting feather. This feather was called a 'pinna' and was used in place of the finger. The Romans made use of the pinna in order to make room for further meals. This was all done without getting up from the table, since the servants would bring forth the vomiting pail when beckoned. Often the pinna alone was not effective; therefore, it was dipped into iris or cypress oil which not only made it more nauseating but also more efficacious."

—George J. D'Angelo. *Surgery, Gynecology & Obstetrics* 101: 247, 1955.

Supplementation of Protein and Caloric Needs in the Surgical Patient

HAROLD G. BARKER, M.D.*

THE IMPORTANCE of adequate nutrition was an infrequently emphasized aspect of the therapy of illness prior to the present century, in spite of the fact that it has been known since 1834¹ that carbohydrate, fat, and protein are the three distinct organic components of food. Practically all of the attention of the 19th century investigators was devoted to the caloric content of food. In 1909 a paper³ appeared on the value of protein in the diet of patients with typhoid fever, and in 1919⁴ experimental work was published on the effect of diet on wound healing. In 1936 Cuthbertson⁵ described negative nitrogen balance in patients with fractures, and Howard *et al.*⁶ later confirmed this work. In 1937 Rose⁷ reported that certain of the amino acids should be considered as "essential" in the diet and others as "nonessential." This contribution was monumental, since earlier workers⁸ had only scratched the surface in this field. His findings, together with those of Cuthbertson, mark the beginning of an era of interest in protein nutrition which has produced many publications and a great deal of careful experimental work.

While adequate nutrition is important in all types of patients, it is the surgical patient who has been the subject of the most attention. This is understandable because many of the clinical situations in which inadequate nutrition has thus far been found to be the most detrimental to the recovery of the patient seem to fall in the field of surgery. Furthermore, the surgical patient is frequently unable to

take nutrition by mouth in adequate amounts. This has led to attempts to supplement the diet by one means or another; and certainly among the earliest methods of supplementation must have been the administration of foodstuffs by rectum. It is now known that little or no absorption of nutrients (except glucose) occurs under these conditions. Nasogastric tube feedings had occasionally been reported earlier, but the method was little used prior to 1916.¹⁰ Jejunal feedings have lost some of the popularity which they had a few years ago, whether this be by direct jejunostomy or by Abbott-Rawson tube.¹¹ The use of the subcutaneous route is also losing favor, particularly since the demonstration that subcutaneous depots can attract more fluid out of the blood stream.¹² Early attempts to furnish nutrition intravenously were fraught with difficulty because of untoward reactions. It was not until 1923¹³ that it became possible to prepare pyrogen-free solutions. It was another 10 years after this before intravenous glucose administration became popular, although it had been known for some time^{14,15} that when glucose is infused intravenously, it disappears from the blood stream without being lost in the urine. Although there had been sporadic reports of various protein substances being infused intravenously, this practice did not become practical until after 1939 when Elman published his experiences with its clinical use.¹⁶ Finally, fat emulsions were administered intravenously to humans by Holt, and co-workers¹⁷ as early as 1935 (and even earlier by Yamakawa¹⁸), but these substances have not yet been sufficiently perfected to lead to commercial production.

NUTRITIONAL REQUIREMENTS IN SURGICAL PATIENTS

Since body stores of fat and protein can be

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called upon to furnish calories temporarily, it must be assumed, when discussing nutritional requirements, that reference is to exogenous sources necessary to maintain balance. It is also well to discuss first the "basal" requirements of the healthy human subject at rest. Total caloric needs under these conditions for a person of average body build are about 900 calories per square meter of body surface per day. The obese subject requires a little less than the basal figure and the lean subject a little more, but in a person of average build weighing 60 kg this amounts to about 1600 calories per day.

Although new data are rapidly appearing from numerous investigators, it is still difficult to state the optimal proportion of carbohydrate, fat, and protein which the diet should contain. Elman has recently reviewed this subject.¹⁹ If the total basal requirement for calories were to be met with glucose alone, it would require about 400 g per day for the person of average size (1.73 square meters of body surface). On such an intake the patient would, of course, be in negative nitrogen balance. It has been determined²⁰ that for short periods of a few days in well-nourished patients nothing is gained in terms of protein sparing by increasing the daily glucose intake above 100 g. Under these circumstances the remaining caloric need is furnished by endogenous sources. It would seem, therefore, that in patients who are being maintained on a protein-free intake, one should always give at least 400 calories daily to keep loss of body protein at a minimum. There is also evidence²¹ that a daily intake of 100 g of glucose is sufficient to prevent ketosis. In the undernourished patient, or when parenteral therapy is to be maintained beyond about seven days, negative nitrogen balance increases unless a higher caloric intake is provided.¹⁹

If negative nitrogen balance is not merely to be kept to a minimum, but rather is to be abolished altogether, it is necessary, of course, to administer protein. In the normally nourished individual it is not wise to give a subnormal caloric intake lest most of the protein be utilized for energy rather than for rebuilding body tissue. However, it has been demon-

strated²²⁻²⁵ that in the presence of severe malnutrition positive nitrogen balance can be achieved even with a deficient caloric intake. The inclusion of potassium in the intake is probably necessary in order to achieve positive nitrogen balance.²⁶ The smallest permissible daily protein intake compatible with good health is probably about 0.5 g per kg of body weight,^{27,28} although this is only half of the usual daily recommended allowance. Only about 6.4 g of purified essential amino acids in the right proportions need be given to an average-sized subject in 24 hours in order to furnish the minimum requirement of the eight essential amino acids,²⁹ the remainder of the protein intake being required to furnish the building blocks for the synthesis of the non-essential amino acids.

Much of what has been said with respect to minimal daily requirements in the basal state requires revision upward when dealing with the ill surgical patient, and here the requirements cannot be stated with the same degree of accuracy. Although the daily expenditure of calories is decreased in malnutrition,³⁰ it is the goal of the clinician to replete such a patient. Once this is under way, as much as 5000 or more calories and 200 or more g of protein per day may be assimilated.¹⁹ The caloric requirements of an average-sized patient with fever increase by about 100 calories per day for each degree Fahrenheit of fever. The caloric needs are elevated in hyperthyroidism and in burn patients³¹ but are reduced in shock and probably little altered by surgical operations *per se*.¹⁹

ETIOLOGY OF NUTRITIONAL DEFICIENCY IN SURGICAL PATIENTS

It is logical to classify the causes of nutritional deficiency into five major categories, as Ravdin³² has done. Insufficient intake is statistically probably the most frequent cause of nutritional deficiency.³³ Not only the quantity but also the quality of protein intake is important, in order that none of the essential amino acids be omitted. Equally important with intake is the ability of the patient to digest and absorb the ingested food. Obvious impairments in this ability occur in

diseases of the gastrointestinal tract either due to direct loss through diarrhea, vomiting, or fistulous openings, or due to deficient secretory activity of digestive glands. The third cause of nutritional deficiency is impaired liver function, so that protein synthesis is inadequate. This is a particularly prominent feature in patients with cirrhosis of the liver but is also seen in acute hepatitis and other liver diseases. Another disturbance which can lead to malnutrition is failure to increase the intake in the presence of an increased basal metabolic rate such as occurs in fever and hyperthyroidism. The fifth and frequently most troublesome cause of poor nutrition in surgical patients is increased loss of protein from the body. This subject has been dealt with in some detail in the review by Lund and Levenson.³⁴ Direct losses obviously occur in hemorrhage, paracentesis, diarrhea, vomiting, and from fistulas, intestinal suction drainage tubes, and large wound surfaces uncovered by epithelium. More subtle but frequently very large losses occur in the urine following burns, fractures, infection, or trauma of any kind resulting in extensive tissue destruction. Protein losses occasionally can be large in the presence of primary renal disease. Rhoads³⁵ has collected from the literature some of the figures showing the magnitude of protein losses in surgical patients.

EFFECTS OF PROTEIN DEFICIENCY

Perhaps the earliest paper demonstrating the importance of nutrition in dealing with specific surgical problems was that of Clark⁴ in 1919 on the healing of wounds. This was followed by the work of Harvey and Howes³⁶ and then of Thompson, Ravdin, and Frank³⁷ who first studied the problem in humans. These authors, together with many who have followed, demonstrated the now well-known fact that in malnourished patients wounds heal poorly and that this is particularly true when protein deficiency has progressed to the point of actual hypoproteinemia. This, of course, points up the fact that whenever possible poorly nourished patients should be repleted preoperatively, and that patients who

are having difficulty with wound healing, including decubitus ulcers,³⁸ in the postoperative period should receive adequate intakes of protein together with sufficient calories to permit use of the protein for tissue building.³⁹

Edema is another possible effect of protein deficiency, as was first pointed out by Jones and Eaton.⁴⁰ The edema need not be manifest generally but may be restricted to an operative site, thus at times explaining an ill-functioning stoma at the site of anastomosis in gastrointestinal surgery.^{11,41,42} It has been shown that the formation of antibodies, and presumably resistance to infection, is lowered by hypoproteinemia.⁴³ Resistance to hemorrhagic shock is also reduced in the presence of hypoproteinemia.^{44,45} It has been known for a long time⁴⁶ that an adequate carbohydrate intake is helpful in preventing damage to the liver by various noxious agents. More recently it has been demonstrated that adequate protein nutrition serves a similar purpose.⁴⁷ Once present, liver damage then leads to still further protein malnutrition by the reduced ability of the liver to synthesize albumin and prothrombin.

CORRECTION AND PREVENTION OF NUTRITIONAL DEFICIENCY

The indications for nutritional supplementation in the preoperative period are fairly well agreed upon, if one allows for minor variations in the clinical estimation of the situation involved. Factors to be considered are the urgency of the operation, the magnitude of the contemplated procedure, and the degree of the nutritional deficiency. If the patient is able to take nutrition by mouth and elective surgery is planned, a few days of forced feeding, perhaps including one of the protein hydrolysates if anorexia is present, will frequently pay dividends in reduced morbidity and mortality. Special situations, such as obstructive jaundice, chronic ulcerative colitis, cirrhosis of the liver, and others, call for particularly careful nutritional preoperative preparation.

Likewise, there is good agreement that every effort should be made to provide a fully adequate caloric and protein intake to the

postoperative patient who is sustaining large losses or who is unable to take a normal diet by mouth by the seventh or eighth day after operation. The indications for large nutritional supplementation, however, are not nearly as clear in the first few days after operation in a patient who is running a smooth course. Moore⁴⁸ goes so far as to state that a mild weight loss during this period is natural and desirable, and Rhoads⁴⁹ states that there is no evidence to indicate that harm results from a negative nitrogen balance in the early postoperative period. Certainly it would seem that, at least until it becomes easy and safe to give 1600 or more calories per day by vein, there is nothing to be gained by giving the well-nourished patient protein intravenously in the first few days after operation. Furthermore, 400 calories per day in such a patient will be as effective as 1600 calories in sparing endogenous protein utilization; therefore, for the present it would seem that the usual 2.5 liters of 5 per cent dextrose (or 10 per cent levulose) daily are quite satisfactory. On the other hand, the evidence appears to be good that the malnourished patient will lose less body protein or may actually go into positive nitrogen balance when protein is given intravenously, even if the caloric intake is subnormal. Therefore, in such patients, particularly if the malnutrition is extreme or the operation of large magnitude, it would seem logical to provide protein supplementation from the beginning.

There are few if any actual contraindications to nutritional supplementation in surgery, but there are, of course, dangers in the overuse of intravenous fluids, particularly in patients with heart failure or so-called lower nephron nephrosis. In patients with liver damage a moderate fat intake (up to 30 per cent of the total calories) does no harm so long as the protein intake is sufficient. One further precaution is necessary in this connection, however. It has been shown⁵⁰ that following portacaval shunt operations, an excessive protein diet can lead to high blood ammonia levels and to a clinical state which is indistinguishable from hepatic coma. Patients with portal hypertension and extensive portal systemic

collateral vessels are in danger of the same difficulties, but to a lesser degree, because of their numerous spontaneous portacaval shunts. Whether patients with other liver diseases are subject to the same difficulties from protein overdosage is not yet clear, but it is true that many patients with liver disease, whatever the cause, are apt to have slightly higher blood ammonia levels than normal.⁵¹⁻⁵³ The patient in uremia is probably one in whom protein intake should be restricted,⁵⁴ although some of the limitations which were once applied in nephritis have been cast aside.^{55,56}

It has been emphasized by many writers that the oral route is always to be preferred for nutritional supplementation. It is also generally conceded that in the absence of digestive difficulties, whole foods are better than hydrolysates or other elemental forms.⁵⁷ When appetite is the only deterrent to a good intake, the correct psychological approach will at times solve the problem.⁵⁸ When a full caloric intake is required in the patient with a normal intestinal tract but who refuses to eat an adequate diet, between-meal and bedtime supplements of milk or water, enriched with one or another of the numerous commercially available powdered nutrients, can be offered. These mixtures are now quite palatable to the average patient. If this method fails, then nasogastric tube feeding can be used. With the small-diameter plastic tubes now available it is not too uncomfortable if such a tube is left in place 24 hours a day. Perhaps the ideal feeding mixture for these patients is a regular diet which has been homogenized in a large-size blender. This equipment, however, is not widely available and in any case the preparation of such a mixture is troublesome. The powdered nutrients are therefore ordinarily used for tube feeding. It has been shown¹⁰ that it makes no difference so far as nitrogen balance is concerned whether the feeding is given as a continuous 24-hour drip or is injected intermittently. Very high daily intakes of protein (up to 200 g or more) may be reached with tube feeding, and under these conditions an increased fluid intake must be provided, lest azotemia develop.⁵⁹ Pareira and co-workers¹⁰

have developed a tube feeding mixture which they believe is superior to others with regard to incidence of diarrhea and other disturbances which occasionally develop with tube feeding. This mixture was used as the sole source of nutrition in 240 patients. Ninety-three per cent of their patients were entirely free of gastrointestinal disturbances, and it was necessary to discontinue the feedings in only 2 per cent of the subjects.

Where enteral alimentation is not possible or is contraindicated it becomes necessary to use the intravenous route. With modern protein hydrolysates it is safe and easy to administer 50-100 g or more of protein daily. Whether this is necessary or desirable depends upon the nutritional status of the patient and the number of calories which can be given. At the present time it is difficult to give sufficient calories along with the protein to prevent its utilization primarily for energy rather than building of tissues. To give the calories as glucose intravenously requires either the excessive administration of water or the use of a concentrated solution which is not only sclerosing to veins, but is also wasteful from the standpoint of loss in the urine. Intravenous alcohol (7 calories per g) may at times be useful, but its use is not widespread. Fructose probably offers some advantage over glucose when the need for calories is considered, since 10 per cent fructose can be given with less loss in the urine than is the case with glucose. Recent evidence⁶⁰ suggests that the inclusion of glucose in the commercially supplied protein hydrolysate solutions may be diminishing the utilization of the protein due to caramelization which takes place either in the autoclaving or on long standing. This process seems to influence the utilization of the peptides but not of the amino acids in the solution. By adding a sterile glucose solution to a glucose-free hydrolysate just before use, diminished peptide utilization is avoided. The same authors⁶⁰ have shown that simultaneous administration of glucose and protein hydrolysate increases the rate of renal excretion of the amino acids in the hydrolysate. Fructose is less open to criticism in this regard. The increased renal loss of amino

acids, however, must be balanced against the added advantage of protein sparing afforded by the simultaneous administration of calories. From this latter standpoint it is advantageous to administer glucose not only simultaneously with but also immediately prior to the administration of the protein hydrolysate. The renal excretion rate of the peptides is apparently unaffected by the infusion of glucose. This is a particularly interesting observation in view of recent data⁶¹ which suggest that normal digestion carries the protein breakdown only as far as peptides in the gastrointestinal tract and that absorption into the blood stream is in this form:

DEVELOPMENT OF FAT EMULSIONS

Most of the difficulty with complete intravenous alimentation should be over as soon as suitable fat emulsions become available, and this should be in the not too distant future. Not only does fat contribute 9 calories per g, but concentrated solutions are not sclerosing to veins. Rapid progress is being made in the method of preparation of fat emulsions and many persons have already received a variety of types on an experimental basis with variable results. The commonest untoward reaction to fat emulsion is pyrogenic. This is at present an unpredictable event and the exact reason for the reaction is not known. We⁶² have recently tested fat emulsions prepared by two different companies. With one lot we observed a febrile response in almost 100 per cent of the patients, while other investigators were observing a reaction rate of under 20 per cent with material prepared in the same way. With the preparation from another manufacturer we observed virtually no reactions, while the rate at one other institution was reported to have been very high. However, it has been firmly established that fat emulsions can be safely administered intravenously to humans and that the fat thus introduced is utilized by the body. It is reasonable to suppose that the production problems will be solved in the near future and that intravenous high caloric intake will then be commonly available to the surgical patient.

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The Judicious Use of Saline and Glucose Solutions before and after Surgical Operations

By JAMES D. HARDY, M.D.*

THE FACT that an essay should at this time be devoted to the preoperative and postoperative use of saline and glucose solutions attests not only the importance of such measures in modern surgical care but also the fact that there remains some question as to precisely how these solutions should be used. While it is universally acknowledged that the administration of such fluids has had an enormous influence in reducing the mortality associated with surgical operations, it is none the less certain that clinical fluid therapy will be steadily altered to accord with a continuously unfolding knowledge of human physiology.

What are a few of the historical considerations that are implicit in the surgeon's daily use of saline and glucose solutions?

One of the first blood transfusions in man was performed by Dennys in Paris on June 15, 1667.¹ One of the earliest reports of the intravenous infusion of saline solution was that of Latta, published in the *Lancet* in 1831; the infusion was used in the treatment of diarrhea associated with cholera.² Around 1880, Sidney Ringer began to publish his series of papers regarding the fact that so-called physiological salt solution would not preserve exposed or excised tissues in a normal state if the saline solutions were made up merely by adding sodium chloride to tap water.³ This work was later extended by the British physiologist F. S. Locke, but its significance was not clearly appreci-

ated in clinical circles until Jacques Loeb's papers appeared about 1900. Returning from Berne in 1901, Harvey Cushing added further clinical recognition to the importance of balanced salt solutions through a paper entitled "Concerning the Poisonous Effect of Pure Sodium Chloride Solutions upon the Nerve-Muscle Preparation."⁴ Essentially, Cushing showed, through the direct perfusion of the hind leg vessels of a frog with solutions of different ionic content, that pure sodium chloride in a solution of 0.7 per cent abolished the capacity of the muscle to respond to stimulation of its nerves; however, if potassium chloride and calcium chloride were added in certain proportions, the irritability of the muscle was restored and it would respond once again to nerve stimulation. On the basis of these experiments, Cushing urged that intravenous infusions in human beings be composed of balanced salt solutions. This point of view has of course gained additional support as the years have gone by, being of particular importance in pediatric practice. At the cellular level, the disrupting effect of pure isotonic sodium chloride solution can be readily demonstrated in tissue culture preparations.

During the 1930's, in part a result of the demonstration that many of the effects of simple small bowel obstruction could be abolished with adequate amounts of saline administered intravenously, there was a notable preoccupation with various formulae by which to estimate the precise salt and water needs of the dehydrated patient. The rigid use of such guides resulted not infrequently in over-treatment, and there developed the inevitable trend in the direction of giving too little salt. As a result of this philosophy of salt restriction, which was proclaimed throughout the 1940's, many physicians now resolutely infuse salt-free solutions when in fact the pa-

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tient is in serious need of sodium chloride. This practice is particularly prevalent in post-operative fluid therapy, and may lead to water intoxication. Fortunately, the use of isotopes to measure the amounts of water and exchangeable sodium in the body under different clinical circumstances is affording quantitative information which should provide an ever more rational basis for clinical fluid therapy.

PREOPERATIVE TREATMENT

The Dehydrated Patient

The preoperative administration of saline and glucose solutions is governed by the apparent degree of dehydration present and by the proportion of salt loss relative to water loss. Both pure salt loss and pure water loss are clinical rarities. Salt and water are usually lost together, but the salt loss often exceeds the water loss, on a relative basis. Thus, a disproportionately large salt loss will result in a diminished salt content of the extracellular fluid remaining to the patient, rendering it hypotonic (hypo-osmolarity). In therapy, relatively more salt than water will need to be given. On the other hand, relatively more water than salt may have been lost, rendering the remaining extracellular fluid hypertonic (hyper-osmolarity). Under these circumstances, relatively more water than salt will be indicated in therapy.

How may one estimate the amounts and types of replacement fluids required to restore the normal complements of salt and water?

The *volume deficit* may be estimated (not calculated) on the basis of the apparent degree of dehydration as judged from the clinical examination of the individual. The physical findings of dehydration will be dependent largely upon the reduction in the volume of the extracellular fluid and thus, in effect, the therapy will be directed toward restoration of this volume to normal. The cells, too, will usually have lost water, but as yet our methods and knowledge do not permit accurate treatment of cellular deficits. The cells must take what they need from the corrected volume and composition of the extracellular fluid which surrounds them. In contrast to the difficulty

of evaluating the salt concentration of the intracellular fluid, the plasma affords a ready sample of extracellular fluid for analysis.

The following rule of thumb may be used to estimate the volume of fluid that will be required in the treatment of the dehydrated subject. *If the individual appears clinically to be "severely" dehydrated, he has perhaps lost eight per cent of his body weight as water; if "moderately" dehydrated, six per cent; if "mildly" dehydrated, four per cent.*⁵ Thus, a 70-kilogram man who is severely dehydrated has lost approximately six liters ($70 \text{ kg} \times 8\% = 5.6 \text{ liters}$) of fluid. This is the deficit at the time of admission. However, since while this fluid is being infused additional losses will occur in the form of urine, gastric contents, and insensible loss, even more fluid will be required. Nevertheless, the six liters represent the initial *volume deficit*. What *types* of fluids should be included in these six liters? What is the relative salt loss, the *osmolar deficit*?

Whereas the *volume deficit* was judged on the basis of the clinical examination of the patient, the *osmolar deficit* is estimated on the basis of the plasma chemistry values. The following relationship¹ is a useful one: Normally, the milliequivalents of chloride plus the milliequivalents of carbon dioxide combining power give the value of 130 ($\text{Cl } 103 \text{ mEq} + \text{"CO}_2\text{" } 27 \text{ mEq} = 130 \text{ mEq}$). If the sum of these values is appreciably greater than 130, the extracellular fluid remaining to the patient contains a relative excess of salt (hypertonicity, hyper-osmolarity). If this sum is less than 120, the salt concentration in the extracellular fluid is significantly diminished and relatively more salt than water will be needed in the replacement fluids. If the sum is normal (130), isotonic saline solution will form the mainstay of the replacement volume.

Finally, the *acid-base* relationships—the third member of the *volume deficit*, *osmolar deficit*, *acid-base triad*—will indirectly influence the volume of replacement fluid given as water (in the form of 5 or 10 per cent glucose) and saline solutions. For example, in the presence of acidosis isotonic saline solution, containing a physiologic excess of chloride

ions relative to the concentration in plasma (0.85 per cent NaCl solution contains 145 mEq Cl per liter), may not be completely satisfactory. In fact, in the presence of poor renal function an acidosis may be considerably aggravated. This is due to the fact that the 42 mEq of chloride in excess of that contained in a liter of plasma have an effect similar to the infusion of 42 mEq of hydrochloric acid. In the presence of serious acidosis, then, it is preferable to give a portion of the sodium intake in combination with a disposable anion such as bicarbonate (as NaHCO_3) or lactate, rather than a fixed anion such as chloride, which cannot be disposed of through the lungs. A mixture of two parts isotonic sodium chloride and one part isotonic sodium bicarbonate or lactate is satisfactory.

Clinical Example. In brief, let us assume that a 48-year-old man with recurrent small bowel obstruction due to adhesions is admitted and a period of conservative management is contemplated, permitting orderly rehydration. He weighs approximately 60 kilograms and appears markedly dehydrated. The *volume deficit* is, thus, 4800 ml or approximately five liters. A liter of 5 per cent glucose in 0.85 per cent saline solution is begun at the rapid rate of 240 drops (16 ml) per minute. At this speed the infusion of a liter will require one hour. Meanwhile, a sample of blood has been sent to the laboratory, and the plasma chloride level is reported as 70 mEq/L (normal, 103) and the carbon dioxide combining power as 35 mEq/L (normal, 27). The sum of 70 plus 35 is 105 mEq/L (normal, 130). Therefore, this simple laboratory study reveals that the extracellular fluid is hypotonic and that a concentrated salt solution is indicated. Moreover, a degree of metabolic alkalosis likely exists, and the physiologic excess of chloride ions contained in a sodium chloride solution may be expected to diminish this alkalosis. We would next give the patient from 500 to 1000 ml of 3 per cent sodium chloride solution, rechecking the plasma chloride and " CO_2 " levels thereafter. After these two liters of fluid, the remainder of the replacement therapy would usually consist of isotonic saline solu-

tion in 5 per cent glucose. The entire five liters could be given over a 12-hour period, and fluid losses due to suction, urine, and insensible loss could then be replaced during the second 12-hour period, unless earlier operation were considered advisable. (Actually, normal renal function would eventually correct the salt deficit even if only isotonic saline were given, but the use of the hypertonic saline should effect this desired result more rapidly.)

The matter of a potassium deficit would ordinarily not be of practical concern until renal function had been restored, after which its diagnosis and treatment could be managed more satisfactorily. It is to be remembered that a metabolic alkalosis, perhaps due to the vomiting that accompanies pyloric obstruction, may reflect a cellular potassium deficit, and such an acid-base derangement may be further aggravated by the infusion of additional sodium without potassium.^{6,7} Sodium ion will already have entered the cells partially to replace the cellular potassium deficit, and the infusion of sodium chloride may force additional amounts of sodium into the cells, further delaying rectification of the acid-base imbalance. While experimental proof of serious organic cardiac damage in human beings is lacking, potassium-deficient animals who receive only sodium chloride may exhibit necrosis of the myocardium at autopsy.⁸ A balanced electrolytic composition in body fluids is, of course, essential for normal electrical activity of the heart.

POSTOPERATIVE TREATMENT

Physiologic Considerations

Postoperative Renal Function. It has been shown that sodium, chloride, and water are excreted at a temporarily diminished rate in the early postoperative period. This is probably due to the net effect of the interaction of the hormones of the posterior pituitary and of the adrenal cortex upon renal tubular reabsorption, and upon water and electrolyte distribution between the intracellular and the extracellular fluid compartments. Therefore, since in the immediate postopera-

tive period the kidneys cannot be depended upon to discard what the body does not need and to retain what the body does need, the fluids administered during this period should be carefully selected to meet the actual needs of the patient. In this way water intoxication due to excessive amounts of salt-free fluids, or edema due to excessive amounts of salt-containing fluids, will be avoided.

Gastrointestinal Activity. Various types of experimental evidence are now available to support the traditional clinical evidence that gastrointestinal function is abnormal immediately following operation and other forms of trauma. For this reason, it is generally inadvisable to administer fluids by mouth immediately postoperatively.

The "Routine" Patient without Complications

The administration of saline in even the "routine" patient will vary considerably from one individual to another for a number of reasons. For example, the patient who has had a simple appendectomy need receive perhaps only 5 per cent glucose in water during the day of operation, for on subsequent days he will take fluids by mouth. The same holds true following herniorrhaphy. On the other hand, the patient who has had a cholecystectomy will usually not take fluids by mouth the day of operation and probably will take comparatively little the next day. Some electrolyte-containing solution will be indicated. Moreover, this patient may suffer from the collection of electrolyte-containing fluids in the stomach and it may be necessary to aspirate the stomach with a Levin tube. This aspirated fluid should be replaced with sodium chloride solution. Finally, the patient who has had a gastric resection and who has an in-lying Levin tube will need replacement of the fluid removed by gastric suction, in addition to other losses. Therefore, the amount of saline solution which any particular patient is to receive will depend in part upon what operation he has had.

The age of the patient will also influence the amount of saline solution that he receives. However, despite all the words that have been devoted to the dangers of overloading the

patient with excessive infusion of salt in the postoperative period, the writer is aware of no individuals in reasonably good general physical condition who have been seriously injured by the administration of one or even two liters of saline solution and a liter of 5 per cent glucose in water, if required. In other words, the house officer does not need to be concerned about using somewhat routine therapy in individuals who are not in heart failure and who are on oral alimentation by the second or third day following operation.

One liter of saline solution (0.85 or 0.9 per cent) can be given to virtually anyone without ill effects. This applies to the vast majority of elderly patients also, but it does not apply to infants. It has been repeatedly demonstrated that the capacity of the infant kidney to excrete sodium chloride is diminished. The administration of undue amounts of isotonic saline to these individuals will result in a retention of salt and water as edema.

Specifically, then, how much water and electrolyte may judiciously be given during the first 24 hours to an individual who has had a gastric resection? If excessive sweating due to hot weather is not present, it is our practice to give from 2500 to 3000 ml of fluid during this period, 1000 ml being in the form of isotonic sodium chloride solution and 1500 to 2000 ml being in the form of 5 per cent glucose in water. Of 2500 ml of fluid given, approximately 500 ml will be lost by vaporization from the lungs and another 500 ml through insensible loss from the skin. Approximately 500 ml of fluid will be aspirated with the Levin tube. The remaining liter of fluid will serve to provide water for urine formation. If only 500 ml of urine are excreted during the 24-hour period in which the operation was performed, the patient is still in a positive water balance of only 500 ml, which is of no moment.

In elderly individuals the volume given is rarely more than 2500 ml and often only 2000 ml during the first 24 hours postoperatively. This may result in the patient's being slightly dehydrated, but it is probably more desirable than (theoretically) to overload the circulation. Again, however, in our experience we

have not seen difficulty at any time from the administration of two and one-half liters of fluid (1000 ml as saline solution) to an individual who was not in cardiac or renal failure. During the second 24 hours following operation fluid volumes similar to those outlined above may be used, but they should be modified to take into account the volume of fluid aspirated by the Levin tube and the urine output. If for any reason there has been excessive fluid loss through the Levin tube or from any other source, such drainage should be replaced with an electrolyte-containing solution. On the third postoperative day most patients who do not have complications will be on oral intake and will not need meticulous parenteral fluid therapy. It may be that their intake will not be quite as satisfactory as desired, and in the evening of this period glucose and saline solutions can be given in whatever amounts are considered necessary to supplement the oral intake.

The Patient Whose Fluid Imbalance Had Not Been Corrected Preoperatively

There will be individuals, particularly those with possible strangulation in intestinal obstruction, who entered the hospital severely dehydrated but whose fluid deficit could not be entirely corrected before the necessary operative procedures were performed for the relief of the obstruction or possibly the resection of gangrenous bowel. Replacement fluid therapy should be continued after operation until a reasonably satisfactory state of hydration has been achieved. For example, let us assume that the individual was severely dehydrated at the time he was admitted to the hospital and that he weighed about 60 kilograms. Using the approximation given above (i.e. severe dehydration, 8 per cent of body weight), one might assume that the individual weighing approximately 60 kilograms has lost 8 per cent of his body weight or about five liters of fluid. This is the *volume deficit*.

It will have been inadvisable to attempt to give the patient five liters of fluid intravenously in the two hours that he was in the hospital prior to the operation for the relief

of the intestinal obstruction. Accordingly, the amount of the estimated fluid deficit which it was not possible to give before and during the operation should be continued following the operation. Whether or not this solution be in the form of hypertonic sodium chloride solution (2 or 3 per cent) or an isotonic saline solution will depend upon the concentration of salt found postoperatively in the extracellular fluid. In actual practice we have given relatively little hypertonic saline solution in the early postoperative period.

In addition to overcoming the fluid volume (and salt) deficit which was present at the time our hypothetical patient was admitted with intestinal obstruction, it will be necessary to replace continuing losses by vaporization, gastrointestinal suction, and urine volume. Moreover, in the sodium chloride and, later, glucose therapy, it is to be understood that any significant acidosis will be suitably treated with sodium bicarbonate or sodium lactate solutions, and that potassium deficits will be treated vigorously with intravenous potassium chloride solution in an 0.6 per cent solution or an 0.6 per cent solution of potassium chloride in 0.45 per cent sodium chloride. Alkalosis of significance not corrected with sodium chloride and potassium may be treated with 2 per cent ammonium chloride in 500-ml doses.

The patient with intestinal obstruction has been discussed here because he is an individual who represents an emergency and who will usually need operative intervention. Actually, the most common patient admitted with vomiting who does not require immediate surgery is the individual with pyloric or duodenal obstruction due to malignancy or to a chronic stenosing duodenal ulcer. The fluid deficits in such an individual can be corrected in an orderly fashion and he can be operated upon several days later when the maximum benefits from water and salt replacement and transfusion have been realized.

Nonfunctioning Stoma and Extended Parenteral Feeding

Thus far the discussion has centered around those individuals whose disorder is relieved by

the operation and who are able to resume an oral intake within 48 to 72 hours following the operation. In these patients any reasonably sound program of fluid administration will achieve satisfactory results in the vast majority. It is now in order to consider a condition in which the matter of fluid therapy poses a much more serious problem. Such a situation is encountered when the gastrojejunostomy stoma fails to function over a period of many days following gastric resection.

As soon as it is apparent that the stoma is not functioning adequately every precaution should be taken that will permit an extended period of satisfactory parenteral fluid maintenance. This means that the intake-output recording efforts will be intensified; that if possible the patient will be weighed from time to time, if not every day; and that the daily urine volume and gastric suction volume will be used as guides to the amount of fluid needed, other guides being the daily estimation of the turgor of the skin and the general clinical evaluation. While the evidence of the state of hydration of the patient (physical examination, urine output, and body weight measurements) will indicate the *volume* needs, plasma "CO₂" and chloride analyses performed every second day assist in the maintenance of the proper ionic (*osmolar*) composition of the extracellular fluid. If plasma sodium measurements are available, they also should be used as a guide to the administration of salt solutions. It is not our purpose to discuss potassium therapy, but a potassium deficit of serious magnitude can occur when the bile and pancreatic juice are being lost, and vigorous prophylactic potassium therapy is indicated. The patient should receive from six to twelve grams of potassium chloride per day. Four or five liters of fluid may be required daily—1000 ml to cover insensible losses, at least 1000 ml to replace urine fluid loss, and 2000 ml to replace loss by way of the Levin tube.

Small Bowel Fistula

This is usually a postoperative complication and usually a serious one. The seri-

ousness of the condition rests principally upon the fact that nutritional maintenance of the individual becomes an enormous problem when he cannot be fed by the gastrointestinal route, in the presence of relatively huge fluid losses from the gastrointestinal tract itself. A few statements will suffice.

The patient may lose from six to eight liters of fluid per day by the various routes, chiefly from the small bowel fistulous tract but also, it is to be remembered, from the vaporization from the skin and lungs, and from the urine. For example if the patient loses six liters per day by catheter suction at the site of the small bowel fistula, as collected and measured in a trap bottle, then he must receive eight liters of fluid if he is not gradually to become dehydrated; for a liter of fluid to replace urine will be required and approximately a liter of fluid will be vaporized from the lungs and skin. The electrolyte loss in these patients is a fairly balanced one, and a definite effort should be made to give a balanced solution containing two parts of isotonic sodium chloride solution and one part of 1/6 molar sodium lactate or sodium bicarbonate solution. These patients deserve every possible safeguard, and special solutions are justified and should be constructed. Admittedly, however, many patients are successfully treated with isotonic sodium chloride solution, sodium lactate being given if an acidosis develops despite renal function. If the patient is maintained in reasonably good fluid balance and the site of the fistulous drainage is treated properly, most fistulae will close spontaneously over a period of from one to three weeks.

Water Intoxication

In 1922, Weir, Larson and Rowntree⁹ described convulsions in a patient with diabetes insipidus who was encouraged to continue his accustomed water intake after polyuria and polydipsia had been controlled with pituitary extract. This syndrome was then reproduced in animals by these workers, who demonstrated that seizures were related not only to the amount of water ingested but also to the concentration of extracellular ions. The administration of sodium chloride was shown

either to prevent or to reverse the syndrome.

It was later appreciated that water intoxication (in part, the "low salt syndrome") may be encountered postoperatively in surgical patients. Recently, Zimmermann and Wangersteen¹⁰ have reported a series of 17 surgical patients in whom water intoxication was considered to have occurred in the early postoperative period. The clinical manifestations consisted of convulsive seizures following operation, associated with a dilution of the extracellular electrolytes. In all except one subject the convulsions occurred between 12 and 48 hours after operation, and in most individuals the water balance was strongly positive. The intravenous administration of hypertonic saline was effective in abolishing the symptoms, apparently by the withdrawal of excess water from the cells.

We have treated with hypertonic saline a patient who became comatose while in markedly positive water balance; the lowered plasma sodium and chloride levels and the sensorium responded promptly to the intravenous administration of 3 per cent sodium chloride solution.

While water intoxication is not common in surgical patients, it can be produced in the early postoperative period if only nonelectrolyte solutions are employed when electrolytes are being lost. The combined interaction of the posterior pituitary and adrenocortical hormones diminishes the ability of the patient to excrete a water load at a normal rate, and excessive dilution of the extracellular electrolytes occurs. This results in a movement of water into the cells, which produces the convulsions. The administration of adequate amounts of salt (or of adrenocortical hormones) renders the production of water intoxication most unlikely.

USE OF GLUCOSE SOLUTIONS POSTOPERATIVELY

One of the first needs of the patient in "stress" is for rapidly utilizable fuel, and the infusion of glucose solution assists in supplying this need. In fact, it is our practice to give most electrolytes in a 5 or a 10 per cent glucose solution. In this way a very useful 400 calories in the form of carbohydrate can

be given with the two liters of 5 per cent solution and 800 calories with 10 per cent solutions (ignoring losses due to spillover in the urine). These calories are important not only in providing fuel but also in their protein-sparing action. Liver function and protection also are thought to be enhanced by an intravenous drip of glucose.

In recent years there has been a renewed interest in the use of fructose with, or instead of, glucose. The disaccharide sucrose (ordinary table sugar made from sugar cane or sugar beets) can be hydrolyzed commercially to glucose (otherwise called *d*-glucose or dextrose) and levulose (which is also called fructose). By and large, glucose (dextrose) is used for intravenous infusion. The parent disaccharide sucrose is not readily used by the body when injected in the unhydrolyzed state into the blood stream; it remains in the extracellular compartment and has a dehydrating effect upon the cells, being used particularly to reduce increased intracranial pressure.

Fructose is apparently metabolized more rapidly and more rapidly converted to liver glycogen than is dextrose. When infused at comparable rates it results in lower levels of blood sugar and less urinary spillage. Fructose is metabolized or converted to glycogen in the absence of insulin, but the clinical application of this has not been fully determined. Fructose can be infused at the same rate but at twice the concentration as glucose, with better retention and less disturbance of fluid balance.¹¹

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A Solemn Warning

"I am not mocking, as I am sure you will acknowledge, when I say that you *must* explain to a patient why you are giving him a certain medicine. Over and over again I have noticed that a patient with more than one complaint will come back in a week or so with the wrong one cured unless a careful explanation is given at the beginning as to which one is being treated!"

—Ronald Gibson. *The Lancet* 2: 411, 1955.

Symbolic Requirements

"The Thanksgiving holiday may serve as an illustration of the many ways in which food and emotions are interrelated. There is every reason to doubt that the sudden desire for turkey which overcomes the people of the United States on that day is related to a physiologic need, or to a deficiency not noticeable during the rest of the year. Yet those who must go without turkey and all the traditional trimmings will feel unjustly treated, dissatisfied, and left out. The feeling that every American is entitled to his Thanksgiving turkey is officially recognized and the Armed Forces, and other large institutions supply this viand. Turkey contains no special morale-building vitamin, mineral, or other secret ingredient. Its effect is due to what it stands for, a symbol of home, family, and congenial and abundant living."

—H. Bruch. *Annals of the New York Academy of Sciences* 63: 68, 1955

Jejunal Feeding

By THOMAS E. MACHELLA, M.D.* AND ROBERT G. RAVDIN, M.D.†

JEJUNAL feeding may be resorted to when oral ingestion or intragastric tube feeding are not feasible. It has the important advantage over intravenous alimentation that it enables the patient to take a dietary consisting of all types of nutriments, and usually provides a higher caloric intake and a more positive nitrogen balance. Jejunal feeding is especially indicated to correct malnutrition resulting from obstruction of the outlet of the stomach or duodenum by malignancy or other disease, from failure of a gastroenterostomy stoma to function after gastric resection, and from duodenal fistula; it has also been recommended in the management of gastrocolic fistula. It may also be used in patients with protracted gastric vomiting secondary to diseases of the central nervous system.

PHYSIOLOGIC CONSIDERATIONS

One of the functions of the stomach is that of a reservoir. It normally retains an ingested meal for about $2\frac{1}{2}$ to $3\frac{1}{2}$ hours, depending on its composition, and empties at an estimated rate of 10 ml per minute. During the time the food remains in the stomach it is mixed with gastric secretions and partially digested. In addition, fluid enters the stomach from the blood stream for the dilution of those food substances which possess high osmotic properties so that they are acceptable by the small intestine. The extent to which gastric content may be diluted under certain conditions is indicated by the observations of Ravdin and associates¹ who found that glucose

solutions of various concentrations, when introduced into the stomachs of dogs, were diluted to a volume as much as $2\frac{1}{2}$ times that originally introduced within a period of an hour. Retardation of gastric emptying time in humans as a result of the presence of barium meal mixtures containing 50 per cent glucose was reported by Pendergrass *et al.*,² and as a result of introduction of concentrated meals by Shay and co-workers.³

It has been firmly established that dilution of hypertonic materials introduced into the small intestine occurs in a similar fashion. Abbott, Karr, and Miller⁴ found that the volume of solution aspirated from a loop of human jejunum isolated by means of an intubation procedure increased directly as the concentration of the solution introduced, a 50 ml volume of 43.2 per cent glucose solution increasing to 100 ml in 15 minutes. Considerable increases in volume of solution removed from a loop of jejunum, similarly isolated, following the introduction of a 10 per cent solution of protein hydrolysate or of a saturated solution of sodium sulfate also have been reported.⁵ The dilution of barium mixtures containing hypertonic glucose solutions has been demonstrated radiologically.² "The intestinal stream produced a cloud effect in the jejunum as though the hypertonic solution caused the mucosa to pour out fluid in an attempt to dilute the opaque medium."² The fluid for the dilution enters the lumen from the blood stream of the intestinal wall. Its loss from the vascular system may be reflected in a decrease in blood volume.⁶ In their experiments, Abbott and associates⁴ noted that the propulsive activity of the small intestine increased with concentrations of glucose above 5.4 per cent. An increase in intraluminal pressure and in motility following the introduction of hypertonic solutions has been recently demonstrated.⁷ Thus the introduction of hy-

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pertonic substances into the intestine can give rise to disturbances in physiology, some of which may be reflected in clinical symptoms such as vomiting, manifestations of the dumping syndrome, intestinal cramps, and diarrhea. *Consequently, one of the important considerations in jejunal feeding lies in the osmotic properties of the materials to be introduced. Such materials should be as nearly iso-osmotic as possible, or else they must be administered very slowly.*

Another important consideration of the type of material introduced into the intestine lies in the nature and percentage of fat introduced. For example, whole milk, though having an osmotic pressure approaching that of body fluids, may also give rise to flatulence, cramps, and diarrhea. These have been ascribed to a specific effect of the size of the fat particles⁸; however, an increase in the osmotic properties of the milk which occurs when its proteins are partially digested to smaller molecules may also play a role. *Most patients cannot tolerate more than 6 per cent crude fat for prolonged periods,⁸ though proportions somewhat larger than this may be tolerated if administered in emulsified form.⁹*

METHODS OF ADMINISTERING JEJUNAL FEEDINGS

The choice among the various means of introducing nutrients into the jejunum depends primarily on the indication for so doing. A tube may be passed into the jejunum by the naso-gastric route, via the duodenum if gastro-intestinal continuity is intact; this procedure is an obsolete treatment for duodenal ulcer, and a current one for the management of intractable gastric vomiting on a cerebral basis. A simple single lumen #16 French rubber tube, or one of the more recently available plastic tubes may be used. A 3 mm polyvinyl tube is soft, non-irritating, durable, and inconspicuous, and may be used for long periods without changing. It is not, however, radio-opaque, and cannot be manipulated under fluoroscopic guidance as readily as the rubber tube. Visualization can be accomplished by filling the lumen with a thin barium water suspension and clamping the nasal end. The attachment

of a small mercury-filled rubber bag by means of a silk suture threaded through the lumen of the tube will aid in the passage of the tip of the tube into the jejunum.¹⁰ A hypodermic needle hole at the proximal end of the bag prevents the accumulation and expansion of gases, tending to keep the tube from being propelled downstream.

This technique may also be attempted in the management of a non-functioning gastro-enterostomy, passing the tube directly through the anastomosis. Unless the tube is put in position at the time the anastomosis is fashioned, however, it usually proves exceedingly difficult to pass when it is needed most. This is also true of duodenal fistula.

In general, therefore, jejunostomy is an operative procedure. With the abdomen open, the very great advantages in keeping the tube out of the oropharynx and esophagus, when it is likely to be in place for a considerable period, lead the surgeon to exteriorize it through the abdominal wall.

The tube may be introduced directly into the jejunum by the Stamm or Witzel¹¹ technique, or it may be inserted into the stomach and threaded into the jejunum, a method of particular advantage when the double lumen tube is used. In either event, the operation is basically a simple one and should not be complicated by elaborations. Local anesthesia may be used in a poor-risk patient. Any incision allowing the surgeon to identify the ligament of Treitz will give satisfactory exposure, but in view of the poor nutritional status of most of these patients, an incision should be chosen which will heal satisfactorily and be unlikely to disrupt. Reopening the previous wound is advantageous particularly in the case of non-functioning gastroenterostomy. A mushroom or bulbed catheter is unnecessary and increases the probability of partial obstruction. For a direct jejunostomy, the first segment of jejunum which will lie comfortably against the left upper abdominal wall is selected, the tube is introduced distally for a distance of 10 to 15 cm and secured by purse-string suture or a short Witzel canal; it is then brought out through a stab wound, drawing the jejunum up to the parietal peritoneum, and

secured at the skin. When the double lumen tube is placed through a gastroenterostomy, the jejunum need not be opened. A gastrotomy is performed to inspect and palpate the stoma, any indicated unkinking is done, and the tube passed through into the intestine. Care should be taken that the holes in the proximal limb lie entirely within the stomach, so as to prevent leakage, and at the same time the tube must not be kinked by an excessive loop.

Such jejunostomies will close within 24 to 48 hours after removal of the tube. Although it has been suggested by Allen and Welch¹² that a jejunostomy be established at the time of gastrectomy, we have not used this operation as routine practice, feeling that it introduces a superfluous procedure in the vast majority of patients, and may, if used prematurely, delay the patient's alimentation by the normal route. For the same reason we abandoned some years ago the routine use of the double lumen tube passed through the anastomosis, with suction on the proximal limb and feeding on the jejunal side. This tube, however, is of great advantage in two situations: first, where the patient's nutritional condition is poor, so that the assurance of the ability to feed within a short interval after operation is more important than any impairment in the immediate function of the gastroenterostomy that may occur as a result of the use of the tube; and second, in the gastroenterostomy that fails to open. In the first instance, the tube is placed at the original operation either through the nose or directly through the abdominal wall; alternatively, a direct jejunostomy may be employed, with naso-gastric suction on a separate tube.

Non-functioning gastroenterostomy, however, poses a serious and challenging problem to the surgeon. The urge to intervene must be strongly resisted, since mechanical difficulties will rarely be found; it is our practice to wait at least three weeks in the average patient before considering re-operation. During this period the stomach should be kept empty, by continuous or periodic aspiration, and the fluid and electrolyte replaced. Gastric distension in itself will interfere with the opening of the

stoma. Trials of oral feeding will of course be necessary, and attempts may be made to get a nasal tube into the efferent loop. Unfortunately, when fluid will not pass into the jejunum, a tube will rarely do so. In the few cases where exploration becomes mandatory, the double lumen tube of Abbott and Rawson¹³ gives splendid results. The tube is so constructed that one limb may be used to aspirate gastric secretions and drainage from the afferent loop, and the other to introduce material into the jejunum, both foodstuffs and the aspirated digestive juices.

In other situations a direct jejunostomy may be advantageously combined with another operative procedure. In a patient with a ruptured esophagus, for example, material introduced into the stomach will commonly drain through the established thoracic esophageal fistula, tending to keep it open; feeding by jejunostomy offers the only alternative to division of the cardiac end of the stomach. We have treated several cases of duodenal fistula by performing a limited subtotal gastrectomy or even an exclusion procedure, placing a tube for aspiration in the duodenal stump, and using a jejunostomy for the return of the duodenal secretions and for alimentation until the gastroenterostomy is functioning.

TYPE OF FEEDINGS

The type of material to be introduced into the jejunum should be non-irritating, approximately neutral in reaction, free of harmful bacteria or their toxins, and should provide calories and the essential vitamins and minerals in adequate amounts. It should be inexpensive and readily prepared, easily digested and absorbed, and capable of being varied to meet individual requirements. It should not be excessively hypertonic and when unavoidably so, must be dripped in at a slow rate in order to avoid the undesirable sequelae of too rapid entrance of hypertonic material into the small intestine. The feeding should be of low enough viscosity to drip by gravity through the tube.

Food mixtures which can be administered vary from ingredients obtainable in most household kitchens to special commercially

available preparations. Some of the latter are considerably less expensive calorie for calorie than ordinary foods and can be prepared more conveniently and in a shorter period of time. In order to obtain consistently good results with jejunal feeding, individual differences may require variation in mixtures and schedules.

Assuming that the patient who is to be fed by jejunum has just been subjected to operation and has a jejunostomy opening for this purpose, the regimen as outlined by Boles and Zollinger,⁸ subject to modification when indicated, may be employed:

(1) *First day:* For 12 to 18 hours after creation of the jejunostomy, nothing is introduced into the tube.

(2) *Second day:* During the second day 50 ml of a 5 per cent solution of glucose in water are introduced at hourly intervals.

(3) *Third day and thereafter:* By the third day, 100 ml of the 5 per cent glucose solution are usually tolerated at hourly intervals. When bowel activity has been restored as evidenced by presence of intestinal peristalsis on auscultation, consideration can be given to the administration of milk. Although whole milk introduced directly into the jejunum may produce cramps and diarrhea, homogenized milk may be better tolerated, presumably because of the relatively minute fat particles.⁸ Starting with quantities of 50 ml of milk hourly, the amount is gradually increased during the next 1 to 3 days to 200 ml every three hours. The administration of water, glucose, and important electrolytes is continued.

Additional calories may be administered in the form of fat, carbohydrate, and protein, depending on indications.

Fat

Attempts to increase the caloric content of the feedings by increasing the percentage of fat usually fail. Most patients cannot tolerate more than 6 per cent crude fat for prolonged periods.⁸ The amount of fat which can be tolerated may occasionally be increased by administering it in emulsified form,⁹ but when so administered it should be given by slow drip.

Carbohydrate

Additional carbohydrate can be supplied by adding 60 g of hydrolyzed starch to each 1000 ml of milk. It is preferable to use carbohydrate in the form of starch hydrolysate or Dextrimaltose,⁸ as these substances are less osmotically active than equivalent concentrations of glucose or sucrose solutions. The latter are tolerated if iso-osmotic concentrations of 5 per cent are not exceeded; when they are, they may have to be administered by slow drip.

Protein

Additional protein may be supplied by adding 60 g of protein hydrolysate to each 1000 ml of milk. If the resulting mixture of milk, starch hydrolysate, and protein hydrolysate when introduced into the tube in large amounts, i.e. 200 ml every 3 hours, causes abdominal cramps and diarrhea, a continuous drip at a slow rate should be instituted, the number of drops per minute being determined by the way the mixture is tolerated. Usually a rate of 40 drops or less per minute is satisfactory.

Vitamins

The caloric intake should be supplemented with the daily requirement of vitamins as recommended by the Food and Nutrition Committee of the National Research Council. These should include vitamins A, D, and C, and the members of the B complex. During the period when very little except glucose and water is being administered, vitamin C and the important members of the B complex can be injected parenterally or the contents of a gelatin multivitamin capsule can be added to the solutions being introduced through the tube. Some satisfactory polyvitamin preparations are available on the market which disperse readily in aqueous solution and can be readily administered through a small bore tube. When intestinal antibiotics are being administered concurrently, vitamin K should be supplemented.

Electrolytes

Feedings of 2000 ml of milk or more will more than meet the daily basic body require-

ments for potassium. But if potassium loss is excessive, or if a deficit exists, 1 g each of potassium citrate, potassium acetate, and potassium bicarbonate dissolved in 8 ml of water can be introduced directly into the jejunostomy tube 3 or 4 times daily. This should replace all but the most abnormal losses of potassium.

Other electrolytes and minerals may be administered when desired, especially if diarrhea is excessive. A convenient preparation available commercially consists of a powder, 80 g of which per quart of water yields electrolytes in terms of mEq per liter as follows: sodium, 50; potassium, 20; calcium, 4; magnesium, 4; citrate, 35; sulfate, 4; chloride, 30; phosphate, 10; and lactate, 4.

Bile

If significant amounts of bile are escaping through an external fistula, about 500 ml of the bile should be properly collected daily and introduced through the jejunostomy tube at intervals.

Low Sodium Regimens

Fresh milk as well as milk powder preparations from which the sodium has been removed are available on the market. These can be used as a source of protein when a low sodium intake is desired.

Other Food Mixtures

Other mixtures are available and can be administered. (a) One readily prepared consists of 4 eggs, 480 ml of light cream, 480 ml of homogenized milk, 70 g of Dextrimaltose® and 150 g of a crude protein preparation such as powdered milk or some of those commercially available. Such a mixture will supply approximately 2400 calories per quart. It is best administered by a slow drip over a period of 12 to 16 hours, in order to avoid abdominal cramps and diarrhea.

(b) A formula which has proved satisfactory in the experience of Stewart *et al.*¹⁴ consists of the following: water, 2000 ml; sucrose, 300 g; casein, 200 g; dried yeast, 30 g; trypsin, 5 g; ascorbic acid, 100 mg; halibut liver oil, 1 g; vitamin K, 4 mg; and salt mixture, 10 g. The salt mixture consists of calcium

carbonate, 20 g; di-hydrogen sodium phosphate, 16 g; potassium chloride, 28 g; magnesium carbonate, 6 g; sodium carbonate, 6 g; ferric ammonium citrate, 6 g; and sodium chloride, 18 g.

The feeding is prepared by adding the casein slowly to the water with the aid of a mechanical mixer. The volume of the mixture is 2355 ml. It contains 78 per cent water by weight, has a specific gravity of 1.068, a pH of 6.2, and has the following proportions of ingredients: total protein, 196.5 g; total fat, 5.08 g; chloride, 3.9 g; sodium, 4.1 g; calcium 1.1 g; phosphorus, 4.7 g; and potassium, 1.9 g. The caloric value of the mixture may be increased by adding fat in the form of cream or of olive or corn oil, though these may cause diarrhea. The mixture is given each day by gravity drip, preferably continuously over a 12-hour period. If the patient is ambulatory, the administration may be made during the night while he is asleep. If the mixture is instilled intermittently, not more than 3 to 4 ounces should be given every half hour during the day. Giving more than this may distend the jejunal loop and cause symptoms. Occasionally the feedings cause diarrhea, in which case reduction in the amount administered, together with administration of paregoric or anticholinergic drugs, may be helpful. At times the mixture has seemed to be constipating.

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Statistical Man

"Statistical man, by definition, is about average in every respect; real men are likely to deviate markedly from the average in many respects. If it were possible to produce a synthetic statistical man, there is no telling what he would be like. Undoubtedly he would be extraordinary; possibly he would lack susceptibility to disease. Real individuals, on the other hand, have peculiarities in metabolism as well as disease susceptibilities, and it seems reasonable to suppose, as a working hypothesis, that the peculiarities and the susceptibilities are closely related. It also seems reasonable to hope, on the basis of the genetotropic concept, that many diseases of obscure etiology can be successfully attacked once we are acquainted with their biochemical nature.

The fact that enzyme levels in the blood are characteristically different for different individuals clearly indicates that the body chemistry of each individual is distinctive. While the total metabolism of each of two men of about average height and weight, measured in calories, may be about the same and very close to that of statistical man, the details of the metabolism of each may be highly distinctive. Some specific chemical reactions may be taking place in one individual ten times as fast as they are in another. If this is true, surely this must be the basis for differences in disease susceptibility."

—R. J. Williams, W. D. Brown, and R. W. Shideler. *Proceedings of the National Academy of Sciences* 41: 619, 1955.

Some Aspects of Nutrition in Pediatric Surgical Patients

By C. EVERETT KOOP, M.D., SC.D. (MED.),* AND R. W. PAUL MELLISH, M.B., B.S.†

NO DISCUSSION of the surgical nutrition of pediatric patients can be divorced from a simultaneous consideration of their fluid and electrolyte requirements as well as other aspects of postoperative care. Perhaps the key to the management of the pediatric surgical patient in this regard is understanding his relatively limited reserve in comparison with an adult. Obviously the differences between adult and pediatric patients are more critical in the young infants and tend to become less important in older children.

In the management of fluid and nutritional problems in neonatal surgery, for example, it must be remembered that the blood volume of a 6½-pound infant is approximately 300 ml. The loss of 30 ml of blood in such a baby is equivalent volumetrically to a hemorrhage of about 600 ml in an adult. Similarly, the infusion of 50 ml into the vascular tree of such a patient would be equal to the infusion of about 700 ml into a 70-kg man. Electrolytes in rather small actual amounts are correspondingly large when considered in relation to daily requirement.

Although definite principles can be outlined for the hydration and nutrition of infants and children, no rules, however carefully set down, can supercede the value of vigilance and frequent re-evaluation of a patient's status and needs. In particular, such care in the pre-

mature infant or newborn of normal weight may mean the difference between life and death. A combination of expert nursing care and watchful supervision by the surgical house staff seems to us to be ideal, for the responsibility rests squarely upon the surgeon who is ultimately responsible for the patient and his care. We do lean heavily, however, upon our pediatric colleagues and particularly on the medical pediatric house staff for aid in the evaluation of patients. It is worth recording that patients being fed parenterally usually present quite different problems on medical and surgical pediatric services. On the former, the indication is usually inordinate fluid and electrolyte loss in a sick infant, while the surgical patient is generally in good nutrition before his surgery and presents primarily a problem in maintenance of normal requirement, with replacement of loss taking a secondary place.

NEONATAL SURGICAL PATIENTS

Surgery of the newborn is almost never elective. Preoperative preparation is sometimes necessary from the standpoint of fluid balance, but not nutritionally. Such preoperative preparation reaches a point of diminishing returns early and seldom takes longer than a few hours. Lesions requiring neonatal surgery are usually those that warrant a venous "cut-down," and we find polyethylene or teflon cannulas to be superior to needles. These may be left in place for several days postoperatively, and usually permit the greater part of parenteral alimentation to be carried out through the original cut-down.

In the first 36 to 48 hours of life, no fluids are given parenterally except to replace abnormal losses. On the first postoperative day fluids are limited to 30 ml/lb and none are given for about 4 to 6 hours postoperatively,

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awaiting readjustment of circulatory dynamics. On the second and third days, fluid intake is increased to 45 ml/lb and to 60 ml/lb on the fourth day. By the fifth day, oral intake is usually adequate but should not fall below 60 ml/lb. Oral feedings should not be forced, however, and intravenous supplements may be necessary. Ideally, a healthy infant takes about 75 ml/lb per day. We prefer a slow intravenous drip around the clock, although some find the administration of divided amounts periodically to be free of the danger of sudden alterations in the rate of flow.

In providing electrolytes, attention is confined to sodium and potassium. The daily requirement of sodium is 0.5 g or $1\frac{1}{2}$ mEq/lb per day. No sodium is used in the first 24 hours after operation and, if plasma is given, its sodium content is calculated as part of this requirement. Once a baby is taking the simplest milk or milk-substitute formula, sodium supplements are not needed. Plasma is given only if a prior deficit has occurred, if suction drainage is in use, or if the infant has been on nothing but parenteral feedings for 48 hours. One mEq/kg per day is the requirement and if there are excessive losses, an upper limit of 3 mEq per day, if given slowly around the clock, provided the urinary output is satisfactory.

Caloric requirements in neonatal nutrition are difficult to meet parenterally, and moderate weight losses are expected on almost any regimen. Usually 10 per cent glucose solution rather than 5 per cent, forms the basis for intravenous fluids, if there is a cut-down in place. When scalp veins are used, infiltration of 10 per cent glucose risks local necrosis. Minimum caloric requirements are 30 cal/kg per day, but considerably more seem necessary for weight gain. Positive nitrogen balance is seldom obtained in this age group. We usually avoid protein hydrolysates, but because of the low weight of these little patients, one can use plasma more economically than in older individuals. A nitrogen intake of 6 ml/lb per day will be satisfactory in most patients. If the hemoglobin is below 13 grams per 100 ml, blood may be substituted for the plasma.

In our earlier experience we frequently used human serum albumin when at least part of the indication was for the treatment of edema, which in retrospect, we believe was due to over-hydration of our patients. If human serum albumin is used, it must be given cautiously in quantities of 2 to 3 ml/kg not more often than twice a day.

It is beyond the scope of this report to go into a detailed description of oral infant feeding, but there will be a section below where some specific principles will be outlined in reference to oral feeding.

Vitamin K is usually given intramuscularly daily, for several days, in doses of 2 to 5 mg per day, and vitamin C is added daily to the intravenous fluids in doses of 100 mg per day. Vitamin B complex is not usually considered to be necessary, but is frequently used if parenteral feedings continue to be used for more than three days. Some multivitamin preparation is given by mouth after oral intake has been established.

INFANTS FROM ONE MONTH OF AGE TO TWENTY-FIVE POUNDS WEIGHT

Much of the surgery in this age group is elective. Where there has been no surgery of the bowel, or where the peritoneal cavity has not been opened except through a hernial sac, little attention need be paid to the temporary dehydration and loss of calories. Clear fluids are usually started by mouth as soon as the patient has fully reacted from his anesthesia, and many patients are back to their pre-operative formulae as early as three to four hours after the end of the operative procedure. Postoperative vomiting, so common in older age groups, is seldom seen in these infants.

If the operation was long or hazardous, a cut-down for intravenous fluids is usually in place and 10 per cent glucose in water may be given by this method until oral intake is established. The rough rule-of-thumb for volume is 30 ml/lb per day, and the rate should not be increased much over what it would be to deliver this amount in a 24-hour period.

Following bowel surgery, the child is frequently quite ill and fluids and electrolytes must be carefully calculated and attention

must be devoted to the caloric intake as well.

Although fluids are restricted to 30 ml/lb per day for the first 24 hours after operation with the replacement of any abnormal loss, on the second postoperative day and thereafter the fluid intake may be increased to 45 ml/lb per day. Some guide may be obtained from the volume of urine excreted as well as its concentration. Ten per cent glucose in water is usually used, bearing in mind the dangers in some infants of local necrosis following extravasation.

The sodium requirements are in the neighborhood of 0.75–1.0 g or 1.2 mEq/lb per day. This should be added to the fluid orders for the second 24-hour period and thereafter. Potassium is not used routinely except after 48 hours of continuous intravenous alimentation, unless a deficit is present. Again, 1 mEq/kg per day meets the requirement, but not more than 3 mEq/kg should be given on one day.

Suction drainage from the stomach or small bowel may be replaced with equal volumes of 10 per cent glucose in half-normal saline. This supplies 75 mEq of sodium per liter, while the content of drainage is usually 40 to 60 mEq per liter. Potassium content of drainage varies from 7 to 20 mEq per liter, depending upon the level of obstruction. These losses may be combatted with the method of sodium and potassium replacement given above, but care should be taken to decrease the potassium replacement as the drainage lessens. When drainage continues for several days and the possibility of partial obstruction exists, or where there is severe ileus, considerable fluid and electrolyte losses may occur into the lumen of the bowel. Blood chemical determinations are very helpful in such patients in planning electrolyte replacement, but until such data are obtained, replacement of measured losses should be with normal saline rather than with half-normal saline. In replacement of electrolytes in such losses, it is not necessary to add the normal daily requirement in the calculations, inasmuch as this represents a relatively small percentage of the total. Obviously, drainage in such patients should be discontinued as soon as it is practicable.

An adequate caloric intake is not particularly easy to assure in children in this age group, even though fluids can be given in greater volume. Starvation and malnutrition are seen in patients in this age group more commonly than in the neonatal group, and the need to supply protein is greater. Here, too, plasma can be given relatively economically and is administered in quantities of 6 ml/lb if there is no circulatory embarrassment. Five ml/kg per hour is a safe rate of infusion, although it can be increased under close observation. Human serum albumin in a 20 per cent solution can also be given in the same dosage as mentioned for the neonatal group. Vitamins are used in the same dosage as indicated previously.

Oral intake can be considered when the passage of a stool or the presence of active peristalsis indicates its safety. First oral feedings are usually glucose-water in this age group in the amount of $\frac{1}{2}$ to 1 oz at intervals of one or two hours to test the child's tolerance. If glucose-water is well tolerated it may be increased in volume and given at three-hour intervals so that the entire normal fluid requirement is being satisfied. Depending upon the condition of the child and the nature of his operation, one can go from glucose-water directly to a formula, or can approach it with an intermediate step of a skimmed milk feeding. Although it is not safe to state that a crying infant needs feeding, the child's reaction is a guide of sorts to the amount and strength of formula that can be given. Usually if the infant sucks avidly and cries between feedings, the amount or the strength of the formula should be increased. Force-feeding should not be done, however, and if the intake falls short of the requirement, supplementary intravenous fluids will be necessary.

STOCK SOLUTIONS OF FLUIDS

Glucose Solutions

Glucose solutions are prepared in concentrations of 5 or 10 per cent in water, normal saline, or half-normal saline. Attention has already been called to the danger of local

necrosis following extravasation of 10 per cent glucose solution, but this fluid is extremely valuable in providing additional caloric intake, particularly in small infants. Half-normal saline solutions are used routinely for the replacement of sodium lost through gastric drainage and for the daily requirements of infants. Where deficits are more marked, normal saline solutions are used instead of half-normal saline.

Electrolyte Solutions

Rarely, hypertonic (2 per cent) saline is needed to replace sodium rapidly in a child who has been neglected before admission to the hospital, or where suction drainage losses have not been properly replaced.

We have found that potassium is conveniently available when prepared as potassium chloride in 50-ml flasks containing 1 mEq/ml. The needed volume can be withdrawn from the flask and introduced into the intravenous fluid container. Except for sodium mentioned above, we at present ignore the remaining electrolytes, although we recognize that their importance is probably considerable in long-term replacement problems.

Plasma

Nonpooled plasma is preferred because of the decreased risk of serum hepatitis. Fresh frozen plasma is sometimes substituted when clotting anomalies are also evident.

Human Serum Albumin

This is supplied as a 20 per cent solution and affords high protein concentration in small volume. The rate of administration must be slow and the total dose kept low because of the increase in blood volume which follows its administration.

Blood

Blood is used in place of plasma when replacement is indicated because of hemorrhage or anemia. Although blood should be typed and cross-matched, we have had a wide experience in urgent emergencies in the use of O-Rh negative blood without any unfortunate accident.

Protein Hydrolysates

We have not employed this form of protein for infants and very small children, but in older children it is a helpful adjunct to protein nutrition. Amigen® is usually given in quantities equal to one-third of the total daily fluid requirement as a minimum, or, in selected patients, can replace the total daily fluid requirement. It is available as 5 or 10 per cent glucose with 3.5 to 10 g of protein per 100 ml. The thrombosis of veins and the presence of a chemical phlebitis after the use of protein hydrolysates makes them of limited usefulness in long-term problems.

Fat Emulsions

Intravenous fat emulsions have been studied in adults and children and they show considerable promise. The lipemia so produced increases the circulating blood volume and therefore the rate of infusion must be carefully controlled. At present, we are not using such fat emulsions except under experimental circumstances.

FORMULAS

The amount and type of formula given an infant is guided by his tolerance and vigor. We use evaporated milk routinely for the basis of most formulas, although we attempt to place our older children on whatever formula they have been accustomed to take. This means a considerable outlay in time, money, and material, but it removes a great many of the headaches of the adjustment of infant formulas to individual tolerances, which is much appreciated on a busy surgical service.

Evaporated Milk

This form of milk contains 20 calories per ounce in standard formulas and may be increased when necessary by adding a carbohydrate such as Dextrimaltose® or red-label Karo.® A standard formula is evaporated milk 13 oz, water 17 oz, and Dextrimaltose #1, 4 tablespoons. Any modification of this formula can be used for individual needs, and occasionally a 1:1 formula in reference to evaporated milk and water is necessary to get an infant to gain weight.

Skimmed Milk

Skimmed milk contains 10 calories per ounce and is given as an intermediate step between glucose-water and a regular formula. In children where fat does not seem to be well tolerated, we sometimes go from glucose-water to skimmed milk, then to half skimmed milk, before placing the child on a standard formula.

Alacta®

This preparation has proved valuable for cases of neonatal bowel surgery, as they seem to tolerate it better than evaporated milk. It is made up of one part Alacta to two parts of water, which preparation then contains 20 calories per ounce. It is approximately equivalent to half skimmed milk in fat content and its caloric value can be increased by the addition of Dextrimaltose.

Nutramigen®

This protein hydrolysate with added fat is reconstituted by adding one part of Nutramigen to two parts of water to form a suspension of 20 calories per ounce. It may be used in a more dilute form as a first feeding. It is used to advantage where milk protein is not tolerated and in patients with pancreatic fibrosis, by whom milk formulas are not tolerated because of the lack of pancreatic enzyme. Diarrhea is a frequent complication with this formula and should be corrected early by a change in formula.

Mulsoy®

Mulsoy is a powder derived from the soya bean and is used in the proportion of 1:2 with water; it is occasionally necessary where milk allergy is a factor and Nutramigen is not tolerated.

A variety of other prepared formulas are available and are used if the infant has been accustomed to them.

Gavage Feedings

Many of the above formulas are used by gavage in patients who cannot or will not swallow, where supplementary feedings are necessary in a sick baby, or where it is pre-

ferred to have the baby fed without the air swallowing common with nipple feeding.

In older children on gavage feedings where frequent stools follow material such as Nutramigen, the addition of small amounts of cornstarch or gelatin to the formula seems to reduce this tendency and to permit normal intestinal transit. In older children where a high protein intake is indicated, such as in recovery from chronic malnutrition or in the nutritional management of burns, gastrostomy formulas which have been effective in adults are quite satisfactory for children also.

TECHNIQUES

Intravenous Therapy

Almost all surgery in the neonatal period is "major," and as a rule a cut-down is placed in an ankle vein or occasionally in an arm vein, if this is more convenient because of operative procedures on the buttocks or lower extremities; and a plastic tube is inserted and tied in place. We prefer plastic tubing to needles and use between a 19- and 22-gauge. This cut-down can be utilized for the administration of blood or plasma during the operation, as well as for parenteral alimentation thereafter. This procedure should be done immediately before the operation so that it will be available for a long period thereafter. Great care must be taken in strapping children to arm-boards for this purpose because of their thin skin and the ease with which it undergoes pressure necrosis. We insert a sponge-rubber padding between an arm or leg board and the child's extremity. Some type of two-way stopcock is attached to the cannula inserted in the polyethylene tubing so that a variety of fluids may be administered and a "push" transfusion undertaken when necessary. A chemical type of thrombophlebitis almost always results following cannulation of leg veins at the ankle if the plastic catheter is left in place for more than 48 hours. We remove such an indwelling tube at 36 hours unless we can foretell a long period when a cut-down will be necessary and the disadvantage of the chemical phlebitis is outweighed by the need for available veins. In older children with adequate arm or leg veins for the insertion of a needle, there is no

need for a cut-down except in procedures where sudden blood loss may be hazardous.

Oral Feeding

Perhaps the cardinal rule for feeding an infant is not to force him. Vomiting should be reported immediately to the surgical staff if it occurs when oral alimentation is being established. This is of particular importance in patients undergoing neonatal surgery. Infants should never be fed when restrained in bed on their backs because of the danger of aspiration of vomitus. If at all possible, infants should be placed in the prone position, following feeding, to lessen the likelihood of pulmonary aspiration of vomitus.

The time spent in feeding is worth mentioning. Neonatal infants should not be allowed to spend too much time at the bottle. If they cannot suck well enough to take a feeding in less than 20 minutes, the frequency may have to be increased or one may resort to gavage supplements. Feeding periods longer than 20 minutes exhaust weak babies and this exhaustion is to be avoided at all cost. Usually a three-hour interval is best for small babies, but if they take their feedings very well, the interval may be increased to four hours as it affords a longer rest period between feedings and requires less nursing care.

Gavage Feeding Methods

Fine polyethylene tubes can carry gavage feedings to the stomach without taking up much of the lumen of the esophagus and are very well tolerated. The open end of the tube protruding from the external nares should never be closed so that it might act as a safety valve. If the open end of the tube is kept several inches above the level of the infant, the feeding will not run out, but gas and fluid under pressure will be able to escape. Aspiration is a definite hazard with the tube in place. For small babies it is best to remove it after each gavage feeding if possible, but in older infants it may be left in place between feedings.

Weighing

Daily weight should be obtained on all children below 18 months of age. Such weigh-

ing should be done on the same scale each day, at the same time each day, and by competent observers. This reduces as much as possible the factors of human error and scale fluctuation. Very sick infants in an incubator cannot always be weighed, and judgment must be used to decide whether the information to be obtained from weighing the infant is worth the risk of disturbing the patient. Accurate weight records are the best source of information about abnormal fluid loss or gain, as well as a check on the general nutritional status of the patient.

Temperature Control and Metabolism

A low temperature at the end of the operation in a neonatal infant is of no disadvantage, but it should be raised carefully to the ideal range postoperatively. Neonatal infants are kept between 97° and 98° F. Higher temperatures at any age increase metabolic needs and should be controlled by cold environment, cold packs, oxygen tents, and occasionally by the use of aspirin in older children.

Chemistry Determinations

Micromethods greatly facilitate the care of infants when chemical studies are necessary. In microtechniques, a few drops of blood from a heel prick can be taken with minimal trauma and very little loss of blood. A venopuncture is quite traumatic to tiny infants especially because the studies are usually most necessary in the infants least able to withstand further insult. In the care of such infants, macrochemical determinations on blood specimens should be kept at an absolute minimum and should be utilized only when specific direction is needed in the planning of fluid and electrolyte orders. Repeated sampling of infants' blood for macrochemical determinations is a serious drain on the child's blood volume, and requires transfusion after several samplings, which adds an additional hazard to the child's care.

CHILDREN OVER TWENTY-FIVE POUNDS

As a child approaches the age of 18 months or weighs more than 25 pounds, his reserve becomes more flexible and his care can ap-

proach that usually given an adult patient. Although rules-of-thumb are dangerous when followed rigidly, a child 18 months of age or weighing 25 pounds can usually be considered as half an adult. This is particularly true of fluid and electrolyte balance problems. Children of this age group, when well and normal, usually control their own caloric intake on the basis of their appetites. This is the age group, unfortunately, where psychological hazards incident to the separation from family and familiar environment enter the picture. Occasionally, such children when subjected to a hospital experience will not eat because of type of food, the way in which it is served, or the absence of a parent. In such circumstances we usually prefer to add the parent to our problems rather than resort to gavage.

Children of this age group are also in a category where subjective complaints alter their appetite and hence their nutrition. In these children the presence of a parent who can coax an oral intake of adequate amount is a valuable adjunct to therapy, but occasionally gavage feedings are needed.

When parenteral alimentation is necessary, fluid requirements vary roughly between 60 and 75 ml per pound per day but should not exceed 1500 ml for a 24-hour period at about 18 months of age. Sodium and potassium requirements are about the same as indicated previously for the lower age group, and the principles of replacing either fluids or electrolytes lost in suction drainage are not altered in these cases.

In this older age group, protein alimentation by the means of plasma becomes uneconomical and in these children we do use protein hydrolysates when indicated by long-term need for parenteral alimentation.

In the neonatal patients undergoing surgery there is almost no lesion that does not present unique problems in nutrition and postoperative care. Space does not permit an inclusion of variations in problem and technique, but the principles laid down above in reference to fluid administration and provision for nutrition can serve as a guide to be varied by the particular need of the patient with a specific lesion.

On Referring the Patient

"The consultant does not depend so much for his success on these agents [faith, hope, and love], he relies more on the build-up you give him. You know the sort of thing: 'You'll find him a bit abrupt, Mrs. Jones, but don't mind him. He's incredibly clever, and he knows your sort of case inside out.' Mrs. Jones carries with her to the hospital your sympathy and understanding, together with the faith and hope you have given her. She is delighted to share your confidence in this particular consultant and she would positively hate him not to be abrupt. His very abruptness becomes part of the treatment she expects from him."

—Ronald Gibson. *The Lancet* 2: 411, 1955.

Facts and Theories

"The best theory is that which necessitates the minimum number of assumptions to unite the maximum number of facts, since such a theory is most likely to possess the power of assimilating new facts from the unknown without damage to its own structure. Our facts must be correct; our theories need not be if they help us to discover new facts, even if these discoveries necessitate some changes in the structure of the theory."

—H. Selye. *Science* 122: 631, 1955.

Surgery of the Diabetic Patient: Changing Concepts

By WALTER M. BORTZ, II, M.D.,* and EDWARD L. BORTZ, M.D.†

HOW FORTUNATE is the diabetic of today! Compared to his ancestors, his can be a life of level continuity and controlled security. Medicine has gained a fair insight into his disease, and has discovered effective tools to combat its threats. These benefits have been directly translated to the procedure of surgery in the diabetic patient.

Before 1925 diabetic subjects were denied all but the most urgent surgery. The mortality figures echo the "last resort" attitude attendant upon these procedures. In the period 1923 through 1926 the mortality of surgical diabetics at the New England Deaconess Hospital was 11.5 per cent.¹ Many other figures far in excess of this are in the literature.

In those days the patient was sent to the operating room after a prolonged period of starvation, thereby draining all glycogen reserves from the liver. The stresses of anesthesia and surgical manipulation exaggerated the metabolic defects, and, as often as not, precipitated frank coma in the postoperative period. Infection was badly managed; the surgeon's hand was forced only when the body was nearly totally consumed by infection.

Today, the attitude has shifted from the negativity of despair to the positivity of decisive action. Surgical intervention is no longer considered a deadly recourse. In fact, Joslin includes surgery among the modes of diabetic control when he points out that operative steps may alleviate diabetes by removal of infection or by elimination of hyperthyroidism—both notoriously bad factors. Too often in the past, a patient has been denied operative

therapy for related or unrelated indications solely because he was diabetic. This attitude is no longer worthy of the best ideals. Indeed, the diabetic patient can and should be presented to the surgeon in such a status that the management is in nearly every respect identical to that of the nondiabetic. McKittrick and Root² illustrated this in the phrase, "To state that a patient has diabetes gives as little information regarding that patient's fitness for surgery and his prognosis as to say that a nondiabetic has appendicitis."

This new-found capacity to deal effectively with the diabetic patient undergoing surgery is mirrored in the increased incidence of operative procedures in this group. In 1910, 2.8 per thousand admissions at Bellevue Hospital, New York were diabetic, while in 1943 through 1948 the average at the Post Graduate Hospital in New York was 2.1 per hundred.³ Likewise, in 1923, there were only 69 operations on diabetic patients at the Deaconess Hospital, while in 1946 through 1950 there was an average of 466 per year.⁴ Sprague⁵ gives reasons for this: (1) a higher number of diabetic subjects in the general population; (2) the greater longevity of these patients; (3) newly designed surgical techniques enabling procedures previously impossible.

FACTS AND FIGURES

Recent postoperative mortality statistics vary somewhat. The Deaconess Hospital figure is currently under 2 per cent.⁴ In 1947 the Mayo Clinic figure was 2.5 per cent,⁵ identical with Shuman's figures from Temple University Hospital.⁶ Rolland reports 9.8 per cent from the University of Edinburgh Royal Infirmary,⁷ while according to Spoont the rate was 5.7 per cent from the Hospital of the University of Pennsylvania.⁸ The higher percentages in all probability are due to the higher

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age group of the patients and the increased incidents of arteriosclerotic and neoplastic complications. For example, over 50 per cent of the Edinburgh fatalities were over 70 years of age, one fourth were operated upon for gangrene of the leg, and another fourth for malignancy. The above percentages compare favorably with operative mortality figures of nondiabetic patients of the same age group.

Despite the diminution in the absolute hazard incurred upon operating on the patient with diabetes, potentially dangerous situations remain. Various characteristics of the diabetic subject make this so: (1) increased obesity; (2) increased cardiovascular disease; and (3) lessened local and generalized resistance. The importance of obesity is generally appreciated. In Shuman's series⁶ there was some degree of obesity in 52 per cent; and 31 per cent of the serum cholesterol levels taken were elevated. At the Hospital of the University of Pennsylvania,⁸ 27 per cent showed cardiovascular and/or renal disease. Joslin has shown that 70 per cent of those who had had the disease for 15 to 20 years showed some arteriosclerotic manifestation; 40 per cent of these had hypertension.¹ Shuman⁶ found arteriosclerosis in nearly a third, hypertension in 21 per cent. The third factor, that of lessened local and generalized resistance, has probably been over-emphasized. This will be discussed below.

The advent of the antibiotic drugs has diminished the importance of infection, while the relative importance of arteriosclerosis and all its manifestations has increased. Yet the amazing success of surgery in nondiabetic subjects of comparable age groups bids us not despair.

BACKGROUND

The best results are more likely to be obtained in the patient who has been followed for some time by his personal physician or by the clinic. This patient would have his metabolic mosaic charted and documented by experience. In this case there would be some gauge as to his ability to withstand stress and the degree of strain produced by it. In 1939, Standard and associates⁹ from Bellevue Hos-

pital, New York wrote that in the 172 patients who were treated preoperatively in the diabetic clinic of that hospital (of the total group of 474), the postoperative mortality was 6.9 per cent. The mortality for the remainder of the group was 20.8 per cent. Preoperative control is, of course, the ideal situation, and there is a lesson to be learned from it.

Every surgical patient should have a preoperative blood sugar determination. It is unfortunate that many surgical clinics let a single urine sugar test suffice in "ruling out" diabetes. Yet the fact that 14 per cent of Roland's group,⁷ 17 per cent of Spoont's,⁸ and 16 per cent of Shuman's⁶ were first diagnosed on their surgical admission, demonstrates that this possibility is not an infrequent event. Likewise, many of the patients with diabetes coming to surgery are elderly and often have a high renal glucose threshold. Recognition that the surgical patient is diabetic can be a crucial factor in survival. Too often surgical patients lapse into coma for want of a thorough preoperative evaluation.

The precise roles of the physician and surgeon cannot be defined, as each institution has its own peculiar quirks of protocol; however, in our opinion, the internist is no more qualified to perform the technical surgical procedures than the surgeon is to cope with the intricacies of metabolic inadequacy.

HOMEOSTASIS

In 1953, Moore at the Peter Bent Brigham Hospital, made a significant contribution in formulating the phases of bodily changes in surgical convalescence.¹⁰ These four phases are: (1) the adrenergic-corticoid phase which lasts for about five days from the time of operation; (2) the corticoid withdrawal phase, fourth through seventh days; (3) the spontaneous anabolic phase, ninth through thirtieth days; and (4) the fat gain phase. Each is characterized by its own metabolic, electrolyte, and psychic patterns, with the expected degree of overlap.

With this as a guide, anticipation becomes the key factor in management of the surgical patient with diabetes as it is in the nonsurgical patient. In daily dealings with the diabetic

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in the office, the aim is to control the metabolic balance in such a way as to avert vascular deterioration. So it is with the surgical diabetic patient, but here the problem is more acute. It is realized that the body, within certain limitations, responds in a definite pattern. Selye¹¹ has shown histologically, and to a lesser extent, physiologically, the effect of stress upon the pancreas. Surely, much has yet to be revealed in this fascinating field, but experience has already shown the practical import of many interactions of stress and metabolism.

The successful management of these patients rests entirely on the physician's thoroughness in evaluating the patient's status and in anticipating his needs. This generality is broad in concept, but simple in practical application. If therapy is planned in advance of the demand of the situation, complications will rarely ensue, and the entire handling will be simplified.

BASIC PRINCIPLES

All diabetics, whether on insulin or not, are operating at some level of metabolic derangement. This derangement is further aggravated by the assault of the surgical operation. In the adrenergic-corticoid phase, and even into the preoperative period, the blood sugar is elevated. The reasons for this are multiple—the adrenal medulla is activated (i.e., releases epinephrine) initially by anxiety, and shortly thereafter by the alarm response to the surgical procedure. This action is experimentally more apparent in the well-nourished animal where the stock of liver glycogen is acutely and severely depleted. Yet this effect of epinephrine is merely transitory. Perhaps a more important result of the release of epinephrine is its stimulation of the anterior pituitary gland to release ACTH.¹² Already proved experimentally, it awaits proof in man.

The release of ACTH stimulates the secretion of the 11-oxygenated corticoids. These steroids have a depressant action on tissue utilization of carbohydrate and a stimulant effect on gluconeogenesis. The metabolic effects of thyroid and growth hormones are as yet not clearly enough defined to merit inclu-

sion here. The anesthetic may be just another agent in raising the blood sugar, and the use of epinephrine as an adjunct to the anesthetic may serve this purpose also.

The extent to which the overall equilibrium is altered by these reactions depends first on the area of surgical trauma, second, on the preoperative state of the patient, and third, on the efficiency with which the therapist deals with the altered state. If any one of these is sufficiently extreme in its deleterious consequences, the patient is in danger.

It is known that even a minor surgical procedure may precipitate coma if the diabetic patient is unprepared. The surgeon cannot regard the diabetic subject as a normal patient if his liver has not been adequately stocked with glycogen. This is one of the chief hazards of emergency procedures when preoperative stabilization has not been attained: this also applies to the postoperative period when early oral feeding is eagerly sought.

The additional fact that diabetics are prone to gallbladder disease (Pratt³ says one half of diabetic autopsies show gallbladder disease) makes careful evaluation of this aspect necessary. It has also been observed that biliary stasis is poorly tolerated, and if calculi are demonstrated early operation is advisable.

Guardianship of the liver by adequate glycogen stores has prompted some clinics to adopt small carbohydrate feedings the morning of operation if at all possible, and to repeat this postoperatively.⁷ This is a far cry from 25 years ago when the patient was wheeled to the operating room with a liver of negligible glycogen content.

Another principle has but recently been elucidated, but its importance is rapidly gaining awareness. Rhoads¹³ has clearly demonstrated that the rate of wound healing is directly related to the availability of protein. In phases (1) and (2) of Moore's scheme¹⁰ a negative nitrogen balance is present. If infection supervenes, this adds an extra power to this component. However, the principle agents held responsible for this at present are the adrenal corticoids. Their gluconeogenic effect is well established. With the already embarrassed metabolism of the diabetic pa-

tient, this assumes increased importance. Insulin, on the other hand, has come to be known as a protein-sparing hormone, and certainly there is no condition in which this is more crucial than in the diabetic subject undergoing surgery. Increasing evidence indicates that contrary to previously conceived notions, diabetes *per se* does not imply delayed wound healing. However, inherent in this conclusion is adequate pre- and postoperative control of the diabetes. Thus, it follows that if the blood sugar level is well controlled, if infection is prevented, and if early oral feedings are instituted, there is no reason to expect prolonged confinement because of delayed wound healing.^{5,8}

In recent years the idea that hypoglycemia must be strenuously avoided has been widely disseminated. It is claimed that in patients over fifty years of age, blood sugars under 100 mg per 100 ml may predispose to myocardial damage. Certainly, an awareness of this possibility is necessary. However, in practice this is an extremely rare occurrence and in reality may be merely coincidence. First, the elderly patient with diabetes is usually of the "stable" type, with a wide margin of reserve. Second, it is adequately established that the arc of their blood sugar swing is quite narrow and they are rarely supersensitive to insulin.

PRACTICAL MANAGEMENT

With this background, a logical sequence of practical management is herewith offered. While there are relatively few basic principles involved, they underlie all further considerations: (1) the patient's weight; (2) age; (3) duration (type) of diabetes; (4) presence of infection; and (5) severity of surgery. Each factor will modify management.

Pratt lists the following hazards in actual handling: vomiting; diarrhea and hyperperistalsis; starvation; dehydration; acidosis; infection; impairment of liver function; vascular disease.³ It is immediately apparent that these are not dangers peculiar to the diabetic patient. Yet the clinician must be particularly alert to these derangements in planning the details of his handling.

As the diabetic patient enters the hospital for an elective operative procedure it is to be hoped that he has received previous attention for his metabolic disorder, as illustrated above. The records from the clinic or physician's office will aid in the period of preoperative stabilization. Each patient deserves a blood sugar and possibly a serum protein determination, and if control is not present, the blood sugar level should be measured three times daily until equilibrium is established. If the patient is taking insulin (approximately 60 per cent of such cases are), he should be maintained on the same dosage as before. If diet alone suffices, so much the better. The diet should be ample in protein and carbohydrate and calories should be determined by the patient's needs. One and a half to two grams per kilogram body weight of protein daily, and at least 200 grams of carbohydrate (300 if toxic thyroid or biliary tract diseases are present) are advised. The foods should be palatable and simple to lessen the hazards of nausea and vomiting. The urine should be clear of sugar and the blood sugar should not exceed 150 mg per 100 ml. Vitamin supplements are given if need be, and small blood transfusions are advised in some clinics for that group (about 30 per cent) who have hemoglobin levels below 12 g per 100 ml.

The procedure on the day of operation varies considerably. What is important is that it be a well thought out regime providing for seeing the patient as a human being and not merely as a data sheet. As stated before, some workers almost routinely feed a small carbohydrate meal three hours preoperatively. There is certainly virtue in this, but in the great number of cases this is not feasible. As a rule, "nothing by mouth after midnight" is standard. If the operation is relatively minor, a glass (150 ml) of orange juice in the morning is in order. An early hour is advisable for the operation, as it facilitates handling of the patient's needs for the remainder of the day. Patients taking insulin should be transferred from the longer-acting insulins to regular short-acting insulin, and during the day of operation a corresponding or slightly higher number of units is advisable. If the proce-

dure is a relatively small one, the patient need not be changed from the long-acting insulin to the regular at all; in this instance he should be given approximately two-thirds the calculated daily dose preoperatively. This should be supplemented with regular insulin later in the day.

For major surgery, the patient is given approximately one-third of his usual daily total dose one to three hours preoperatively. Patients taking no insulin previously may be given ten units of regular insulin preoperatively. This dosage is an arbitrary figure and is individualized according to the factors enumerated above. It is best not to overmedicate and oversedate elderly patients preoperatively, as they withstand anoxia relatively poorly. Fluid orders are written as they would be for the nondiabetic patient. An intake of at least 80 grams of carbohydrate by some route that day, is essential. The role of anesthesia will be discussed in a special section.

On return from the operating room, the clinical situation must be carefully evaluated. Insulin should be continued at six-hour intervals until fever subsides or until the adrenocortical phase is nearly spent. If on the afternoon of operation there is uncertainty as to the exact metabolic status, quantitative urine sugar determinations are always the best assaying device. However, the presence of oliguria and the use of intravenous glucose solutions will negate the validity of the blood sugar and the qualitative urine sugar tests. Yet, by equating the number of grams infused versus the grams in the urine the amount of carbohydrate retained may be calculated. The practice of instilling insulin into the infusions is mentioned only to condemn it, because insulin is poorly utilized by this route, and accomplishes its purpose less satisfactorily than when given subcutaneously. Intravenous insulin is indicated only in the presence of shock. Furthermore, with a juvenile diabetic, great caution must be exercised in treating with adequate insulin. It is in this type that precipitous diabetic coma is encountered. Coma and ketosis are preventable and inexcusable in the surgical diabetic patient. Their

presence plainly indicates neglect or ineptitude.

If insulin every six hours (not four times daily) is not sufficient for control, the interval must be shortened. Duncan and Hayward¹⁴ have shown that fever and increased metabolism shorten the duration of activity of insulin. McKim and Fowler¹⁵ state, "The patient should have as much insulin as is required, at the time it is required, regardless of the number of injections and the time of day or night." In any case, mobility of management is of paramount importance. Anticipation of need is inherent in successful postoperative care: the physician does not treat the patient of the moment, he treats the patient of three to six hours thence.

On the day of operation, five per cent glucose in water is practically the standard intravenous solution. If appreciable vomiting occurs, then, of course, various electrolyte solutions must be instituted. If the intravenous route need be maintained longer than 48 hours, it is wise to consider changing to 10 per cent glucose solutions. Incorporation of intravenous protein preparations and vitamins is also advisable. Intravenously administered fructose has been advocated; however, recent evidence shows it offers no advantage. It had been postulated that fructose was metabolized by an insulin-sparing pathway, but it now appears that multiple pathways exist, and, in reality, insulin is utilized. Physiologic saline solution should be used with caution, for in the adrenergic-cortical phase salt is retained in association with the potassium loss.¹⁰ The use of potassium salts is also advisable if a prolonged course develops. This catabolic phase must be anticipated and treated.

If at all possible, small oral feedings should be attempted late in the afternoon of the day of operation. This is a deliberate attempt to combat the negative balances existing at this time. Ginger ale, tea or coffee, orange juice, oatmeal, gruel, and water are advocated. Overcoming natural aversion to food requires ingenuity. The next morning a fasting blood sugar determination precedes a breakfast of juice, custard, cereal, tea, or coffee. As the appetite returns, a full diet is prescribed, with

at least one gram of protein per kilogram of body weight.

Twice daily blood sugar tests plus fractional urine analyses for the first four to six days are valuable as guides for insulin dosage. If oliguria or anuria develops, more frequent blood sugar analyses may be advisable. Insulin should not be stopped on the basis of several negative qualitative urine determinations. Serum and urine acetone levels are invaluable indices in the presence of infection, for as is sometimes seen, sugar may be inconstant in the urine although protein catabolism is accelerated. With a general knowledge of the patient's condition, the temperature chart, the data sheet, and foreknowledge of the lowering of adrenocortical function regular insulin may be changed back to the longer-acting forms. At times, additional insulin may be required. Also, if the insulin dosage was raised, it may have to be lowered in the corticoid withdrawal phase. In the postoperative stage, blood sugar levels of 180 mg per 100 ml are acceptable; however, sustained levels of over 200 mg per 100 ml are distinctly undesirable. Parenthetically, it may be added that the well-controlled diabetic is no more likely to develop wound infection than the nondiabetic patient.

From the foregoing program, it is evident that the clinician is not overly burdened with therapeutic considerations. He should not resort to the many arbitrarily constructed schemata, which are misleading. Such rigid regimes deny individualization.

As the secretion of corticoids levels off and homeostasis is once again sought by the body, initial imbalances are corrected. Nitrogen balance is no longer negative; sodium is lost and potassium retained; peristalsis returns together with appetite; weight seeks its original plane. The spontaneous anabolic phase heralds metabolic reconstruction. Spont⁸ observed that 70 per cent of patients taking insulin were taking the same amount on return home as on admission, 7 per cent took less, and 23 per cent needed more.

Good nursing care is essential for the diabetic patient undergoing surgery. Inasmuch as many surgical procedures require pro-

longed bed rest, care of the skin is vital, and any skin fissure must be regarded as a potential hazard. Possible sources of elevated temperature must be rapidly sought out and eradicated. Also, because it has been recently observed that the diabetic appears more liable to pulmonary embolism, alertness to this possibility, especially in the obese, is advisable. Joslin¹ preaches, "Keep the diabetic busy getting well." This is of special value in re-establishing vigor, and resurrecting the "up and at 'em" attitude.

EMERGENCY

Emergency surgery on a patient in ketosis is a dangerous procedure. Whereas a high blood sugar level and glucosuria alone would never constitute a valid basis for delaying an emergency procedure, frank acidosis may. The degree of toxicity, the mental status, presence of fever, clues in the history, and evaluation of time-honored physical signs will guide the therapy. Blood is analyzed for sugar, carbon dioxide, and electrolytes; likewise, a blood culture is drawn if septicemia is seriously considered. Twenty to 100 units of regular insulin, half to be administered intravenously and half intramuscularly, are ordered immediately. Antibiotic drugs are given and the metabolic situation is balanced against the surgical indications. It is usually possible to wait several hours, after which time the blood sugar values should be falling and the patient should be rehydrated. Sometimes, waiting will enable a more conservative procedure than was thought possible before. This is especially so in a patient with a gangrenous toe or foot.

It is wise to remember that diabetic acidosis may be a very good mimic of the "acute surgical abdomen." Nausea, vomiting, tenderness, rigidity, tachycardia, and even leukocytosis are features common to both conditions.¹⁶ Pancreatitis and cholecystitis are sometimes imitated, and there are known instances of laparotomies on the acidotic patient. The distinguishing characteristics are dependent solely on a high level of suspicion. The diabetic is more likely to have the vomiting precede the pain, no rectal tenderness, a

more diffuse pain, and other generalized signs which lead to the differentiation.

ANESTHESIA

Much has been written on the use of the various anesthetic agents, and for good reason. In fact, Colwell said in 1947, "Prolonged general anesthesia is a more important factor than surgical manipulation, in that it is more likely to disturb the sugar balance suddenly and violently, possibly by toxic effects on liver function."¹⁷ Nevertheless, anesthesia may be given to the diabetic patient with the same indications as in the nondiabetic. Ether is notoriously bad for the subject with diabetes, both by its sympathomimetic actions and by its tendency to induce nausea and vomiting. On the other hand, caudal and spinal anesthetics are desirable in that they apparently do not affect the liver. Likewise, good results have been reported with the refrigeration techniques. One must be alert to the possibility of a hypoglycemic episode when the patient is recovering from the anesthesia.

NEW CONCEPTS IN SURGERY

It is generally known that the majority of patients over 50 years of age have demonstrable peripheral vascular disease. In all reported series of operations on diabetics, peripheral vascular complications are frequent. In these patients, all the resources of the physician must be mobilized. The decisions, if and when and where to amputate, involve problems of major dimensions. It is not always wise to avoid operation and it may be better to walk with a wooden leg than to drag a diseased one. The antibiotic drugs have permitted hesitancy in dealing with these problems. The increased armamentarium of therapeutic agents for the protection of the peripheral circulation, together with the newer surgical procedures, will not be elaborated upon here except to note the fine results found in trans-metatarsal amputation. McKittrick and associates¹⁸ report a series of 215 patients, in only 33 of whom did the lesion fail to heal or need higher amputation. Follow-up studies on 174 showed good results in 135, unsatisfactory in only 32.

Further safeguards are anticipated for the diabetic patient who requires surgery as research adds more information concerning the basic metabolic disorders. Surgical methods and new techniques, together with refinements in anesthesia, also promise greater safety when the need for surgery appears.

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Nutritional Rehabilitation of the Elderly Patient Undergoing Surgery

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ELDERLY patients with surgical lesions frequently have serious nutritional problems. The clinical, as well the more frequent and therefore more important, Subclinical deficiencies which so many of them present are a challenge to the surgeon because these deficiencies may produce profound physiological changes. These changes are frequently accentuated in response to the anesthetic agent and the operative procedure. Since surgical morbidity and mortality are considerably less in those patients whose physiological state is normal or nearly normal, every effort should be made to correct any existing abnormalities before operation. Of course, some deficiencies cannot be completely corrected as long as the surgical lesion exists.

Nutritional deficiencies are more frequent in the aged patient for a number of reasons, among which might be listed: (1) decreased zest for life; (2) lack of appetite; (3) inadequate dentures; (4) minor types of "indigestion"; (5) faulty notions about such foods as canned foods; (6) preference for the easily digestible carbohydrate foods; and (7) self-imposed or prescribed special diets. The presence of a disease—an infection, a carcinoma of the intestinal tract, a peptic ulcer, etc.—then adds to the existing malnutrition because of such physiological disturbances as continued bleeding, biliary tract obstruction, disturbed gastrointestinal activity, and increased rate of catabolism associated with elevation of temperature.

It has only recently been demonstrated that the nutritional requirements for the elderly

patient cannot be measured by the accepted standard for adequate nutrition for the young adult.¹ Although by and large the type of preoperative and postoperative nutritional therapy of aged persons does not differ significantly from that required by younger adults, the treatment must be modified, especially in respect to dosage and rate of therapy, in order to keep within the limits of tolerance of the elderly patient's functional reserve of vital organs. Most geriatric patients are similar in this organ function reserve to patients with long-term illness. Part of the aging process can be described as the result of the "insults" of ordinary life, each of which produces some major or minor destruction or alteration of tissue and thereby reduces the functional reserve capacity of the cardiovascular, pulmonary, renal, muscular, hepatic, and other systems. The patient with a long-term illness has repeated or continued serious "insults" to the body, and therefore may be said to "age" faster than a normal individual.

NUTRITIONAL EVALUATION

Evaluation of the nutritional status is reached with the aid of information provided by a history—including a dietary history before and after development of the surgical illness, a physical examination, and information provided by laboratory tests. Every elderly patient scheduled for a major operation must have at least an electrocardiogram, blood urea nitrogen and blood sugar determination, chest roentgenogram, and complete urinalysis and blood count. Additional laboratory examinations are performed as indicated. *If one excludes specific cardiorespiratory function tests, approximately 70 per cent of the tests performed by the hospital chemical laboratory reflect directly or indirectly dietary*

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deficiencies or lack of proper assimilation and metabolism of foodstuffs! Knowing the physiologic disadvantages of the various nutritional deficiencies and the status of the cardiorespiratory, hepatic, and renal functions, one should be able to evaluate to a large extent the patient's ability to tolerate anesthesia and operation.

A marked weight loss, not due to acute dehydration, is a good indication of a protein deficiency—as is muscle atrophy. Weight loss and muscle atrophy usually parallel the degree of protein deficiency. Complete obstructive jaundice for a number of weeks implies the presence of a vitamin K deficiency. The electrocardiogram may indicate not only conductive defects but also suggest thiamine deficiency, hyperpotassemia, and hypopotassemia. Anemia may be the result of an iron, vitamin B₁₂, or protein deficiency.

The evaluation may also make possible a decision as to how limited the physiological reserve of the patient is, and how strenuous the replacement and corrective therapy should be. As stated before, the quality and extent of therapy does not differ in the aged patient from that in a young adult, but the rate or quantity given per unit of time often requires restriction in the aged.

Protein Deficiency

Significant weight loss of more than 10 pounds and/or marked muscle atrophy over weeks or months is almost always an indication of a protein deficiency. Occasionally a patient with a severe protein deficiency will have no weight loss because of the presence of progressive edema, such as was seen in war famine. A deficiency of protein can be a serious handicap to the surgical patient. It leads to a decrease in blood volume (hypovolemia), plasma volume, circulating red blood cell mass, total circulating serum protein, and to other sequelae listed more extensively in Table I.

Although the most practical method of determining the presence of a protein deficiency is by assessing weight loss, a more exact evaluation requires the measurement of blood volume and plasma volume. The Evans Blue

TABLE I
Effects of Protein Deficiency

1. Weight loss
2. Muscle atrophy
3. Anemia
4. Reduced circulating serum protein
5. Hypotension
6. Hypovolemia
7. Poor wound healing
8. Susceptibility to infection
9. Edema
10. Decreased gastrointestinal motility
11. Weakness—fatigability
12. Prolonged convalescence
13. Decreased calcium ion
14. Tendency to acidosis
15. Predisposition to thromboembolism
16. Reduced enzyme activity
a. peptic activity of gastric juice
b. xanthine oxidase activity of liver
c. renal phosphatase
d. succinic dehydrogenase of liver
e. hyaluronidase of testes

dye (T-1824) method of measuring blood and plasma volume has proved to be satisfactory for most clinical purposes.² It should be emphasized that the red blood cell count, hemoglobin concentration, hematocrit value, and serum protein concentration may not be abnormal even when a serious hypovolemia exists. It is interesting to note that Keys and associates have observed in normal men, starved for six months, an average weight loss of 24.5 per cent of the body weight and the development of edema with practically no decrease in the serum protein concentration.³ The data presented in Figure 1 illustrate that the hemoglobin, hematocrit, red blood cell, and serum protein values may not lead one to suspect a protein deficiency, even though a very serious deficiency exists.

Protein Requirements

A patient confined to bed with a febrile illness of more than three days often requires more protein than is provided by the ordinary "routine" hospital diet. Such patients should receive about 150 grams of protein daily.⁴ Burns, intestinal obstruction, open traumatic wounds, ascites, hepatic disease, and renal disease may produce alarming protein losses. Supplementary vitamins and an adequate ca-

loric intake are necessary for protein to be used for repair and replacement of tissue. Without these, protein is not utilized or is burned up to provide calories for metabolic

was decreased to 7 g; an increase of up to 2800 protein-free calories did not produce a further decrease in the nitrogen loss. Furthermore, it was only when a daily intake of 900

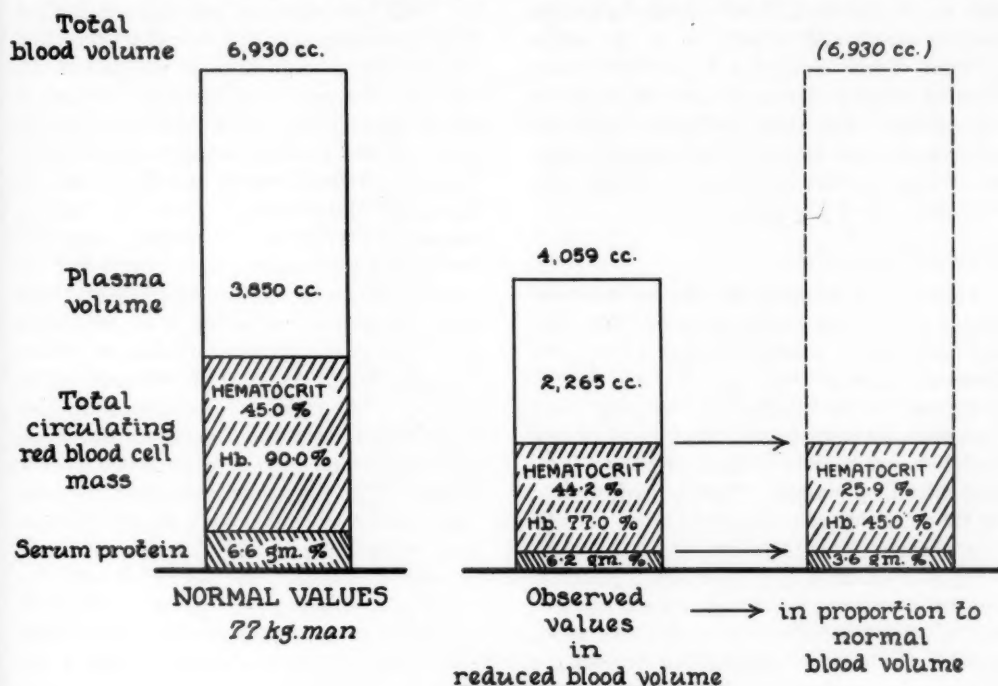


Figure 1

These values illustrate how a serious hypovolemia may exist without appreciable reductions in the hemoglobin, hematocrit, or serum protein values. This patient had had a duodenal ulcer for many years. Symptoms of obstruction were present for only one week. He had vomited twice during the week. His weight was 154 pounds or 77 kg.

The values in the second column indicate those obtained from the patient's blood. The hematocrit value of 44.2%, hemoglobin of 77%, and serum protein concentration of 6.2 g/100 ml are within normal limits for a 58-year-old male. The total blood volume of 4059 ml and the plasma volume of 2265 ml are little more than half the expected values of 6930 ml and 3850 ml, respectively, for this man, shown in column 1. (The actual blood volume deficiency was 2871 ml). If his blood volume were restored to normal with fluid alone, then the hematocrit would be 25.9%, the hemoglobin concentration 45%, and the serum protein concentration 3.6 g/100 ml, as shown in column 3.

The implication, of course, is that such a patient should receive approximately 2500 ml of whole blood before he is subjected to the trauma of anesthesia and major surgery—in this instance, subtotal gastric resection. His nutritional state could not be improved by adequate diet, tube, or intravenous feedings alone.

requirements. Calloway and Spector⁵ wrote an extensive review of the published observations on protein intake in the presence of a reduced calorie intake. They found that in the fasting state approximately 12 g of nitrogen were lost daily. When the food intake consisted of 700 protein-free calories, this loss

calories was achieved that the addition of protein to the diet produced a noticeably less negative nitrogen balance than the same number of protein-free calories. In other words, an intake of 900 nonprotein calories was the lowest level at which the addition of protein to the diet produced noticeably less negative

nitrogen balance than the same number of protein-free calories. Since the average caloric intake of a surgical patient who receives only parenteral fluids is 600 calories, the addition or substitution of fluids containing protein hydrolysate would appear to be a useless gesture. Three liters of a 5 per cent glucose solution provide 150 g of carbohydrate, or 600 calories. Two liters of a 5 per cent glucose solution plus one liter of a 5 per cent glucose—5 per cent protein hydrolysate solution provide only about 825 calories.

Protein Replacement

There can be no doubt that the most efficient use of protein for replenishing and repairing the body tissue results from use of the oral route of administration, provided the gastrointestinal tract is functioning normally. Gastrostomy and jejunostomy feedings of normal foodstuffs are seldom utilized as efficiently as food taken by mouth. Protein hydrolysates by tube and by vein follow in order of relative efficiency of utilization.

Since about 30 g of protein are replaced in the tissues for every gram of protein replaced in the total circulating serum protein, weeks and months may be required to overcome a serious protein deficiency.⁶ Under the most ideal circumstances, with an excellent appetite, no injuries, no infection, no debilitating disease (including no gastrointestinal disturbances), a patient with a protein deficiency indicated by the data in Figure 1 would require from 35 to 40 days to overcome the deficiency. In the presence of a disease he might require two to three times this long and, depending upon the nature of the disease, he might never be able to overcome the protein deficiency. It stands to reason, therefore, that it is useless to talk about overcoming serious protein deficiencies after a week or two of a high protein, high caloric diet. Such a diet will be helpful and should be employed, but frequently it cannot correct the deficiency. Protein hydrolysate preparations for intravenous use are not adequate to maintain positive nitrogen balance in the presence of a serious surgical illness and, therefore, cannot restore body protein. Hydrolysates admin-

istered intravenously or by tube may help, but even this has been questioned. Usually the greatest good within practical limits of time available for preparation for operation will result from adequate transfusions of whole blood in combination with a high protein, high caloric, high vitamin diet—if the patient can ingest it. Restoration of the blood volume to nearly normal by transfusion will obviate many of the serious surgical complications which result from protein deficiency and the associated hypovolemia. Once the surgical disease is eradicated, the patient can, with the aid of a high caloric, high protein diet and adequate fluid and vitamin supplements, overcome the protein deficiency with restoration of the tissue during the convalescent period. Patients who do not have protein deficiencies, anemia, or hypovolemia, of course, should not receive blood transfusion because of the danger of transfusion reaction or of homologous serum jaundice. In the protein-deficient, hypovolemic patient scheduled for a major operation these complications are "calculated" risks. An elderly patient who has no historical or physical evidence of a protein deficiency, should not even be considered for transfusion if he is scheduled for a routine inguinal herniorrhaphy and his hemoglobin value is 70 per cent or above. Anemias due to vitamin B₁₂ or iron deficiency, of course, should be treated with the indicated agent.

In most patients, the equivalent of normal feedings by Levin tube in the form of protein hydrolysate mixtures or of natural foods, tends to produce diarrhea, which is not easily controlled by paregoric and other agents. The diarrhea produces a loss of nutrient material introduced into the gastrointestinal tract. Attempts to feed a high caloric, high protein diet by tube are most frequently met with an increase in diarrhea, with a further increase in the relative loss of nutrient material. In most instances it is fortunate if a patient can maintain his nutritional status on tube feedings, let alone improve. This does not mean that tube feedings should never be prescribed, for an occasional patient will have a gratifying response and, of course, in some patients it is the only method of getting food into the gas-

trointestinal tract. Occasionally, tube feedings are used with excellent results to supplement food eaten by the patient.

It is important to remember that if there is a deficit of whole blood the aged patient will not be harmed and will be benefited by the administration of adequate amounts of whole blood, judiciously administered. The risk of surgical morbidity and mortality will be reduced. It has been suggested that in the absence of an original blood volume measurement, a hematocrit approaching 50 per cent and a hemoglobin approaching 100 per cent are indications of satisfactory whole blood replacement. If as much as 1500 to 2500 ml are required, then each 500-ml transfusion can be administered slowly (in the absence of shock) on a separate day. Occasionally, each transfusion is reduced to 250 ml per day. Pulmonary edema in the absence of cardiac failure will not result from the replacement of whole blood, but it may be produced when the replacement is too rapid. Replacement of whole blood produces insignificant, or more frequently no, elevation of blood pressure in the absence of shock, even in the patient with severe hypertension. Occasionally, whole blood is administered in the presence of cardiac failure, but such a maneuver requires the greatest of finesse, with the added comfort of the presence of a phlebotomy tray.

The author would like to point out an experience with more than 500 operations on patients with severe hypertension subjected to sympathectomy or sympathectomy and adrenalectomy. While operable hypertensive patients cannot be considered elderly patients, certainly these patients have an "aged" cardiovascular system. Many of these patients received from 500 to 2500 ml of whole blood more than was lost during the operative procedure. Only one of these patients developed pulmonary edema, and a few were in frank cardiac failure at the time of operation and transfusion. Relaxation of the vascular tree produced by operation in these patients could not account for the lack of untoward reactions, especially from the larger amounts of blood administered. These patients did not develop pulmonary edema because they had blood vol-

ume deficits and the blood was administered slowly in the absence of shock.

Plasma, serum albumin, and the synthetic plasma volume expanders are all very poor substitutes for whole blood, and, with rare exceptions, they should be used only when whole blood is not available. There is no indication for the administration of red blood cell suspensions to surgical patients unless washed red blood cells are given to the patient who cannot be properly matched with whole blood. Washed red blood cells also are obviously a poor substitute for whole blood.

Vitamin Deficiency

It is good judgment to give every elderly patient supplementary vitamins. A common dietary fault of these older persons is to increase their carbohydrate intake and reduce other portions of the diet, some of which provide thiamine. As is subsequently noted, thiamine is utilized or "consumed" as carbohydrate is metabolized. For these reasons the aged patient is frequently deficient in thiamine. There is evidence to indicate that even when the diet meets the standards suggested by the National Research Council (Table II), many elderly patients will have subclinical or clinical vitamin deficiencies.

TABLE II
A Formula for Standard Vitamin Maintenance*

Thiamine HCl.....	2 mg
Riboflavin	2 mg
Niacinamide	20 mg
Ascorbic acid.....	50 mg
Calcium Pantothenate.....	5 mg
Pyridoxine HCl.....	0.5 mg
Folic Acid.....	0.25 mg
Vitamin B ₁₂	2 µg
Vitamin A.....	5000 Units
Vitamin D.....	400 Units
Vitamin K	2 mg

* From "Therapeutic Nutrition," National Academy of Sciences—National Research Council, Publication 234.

Rafsky and Newman¹ have found apparent improper utilization of vitamins in elderly individuals in spite of the fact that their diets met the suggested vitamin standards and in

spite of the fact that post-ingestion vitamin serum levels were normal. It would seem that the elderly patient does not utilize vitamins adequately even though the vitamins are ingested and absorbed. Thus it appears that the vitamin requirements of apparently normal elderly people cannot be measured by standards acceptable for young adults. In the presence of an illness it has been demonstrated that an additional increment in vitamin intake is required, even when there is no reduction in dietary intake and when there is no disturbance of the gastrointestinal tract.

The importance of an adequate supply of vitamin C for wound healing and vitamin K (and bile salt) for normal blood clotting is well known and will not be discussed in detail. Why should other vitamins be given to patients during an illness? And especially, why should liberal quantities of the individual vitamins be administered to the aged patient?

It has been claimed that vitamin deficiencies may predispose to certain infections.⁷ Vitamins should be prescribed liberally to help control and prevent the development of infection. Thiamine, as previously mentioned, is necessary for the utilization of carbohydrate in the body and is used up at the rate of about 0.5 mg for each 1000 calories. Carbohydrate metabolism may be seriously altered before the development of the clinical signs and symptoms of thiamine deficiency become apparent. According to Sydenstricker,⁸ a patient may develop a thiamine deficiency in as short a period of time as 4 or 5 days when the only nutrient material is intravenous glucose.

The suggested daily intakes, or maintenance dosages of the known vitamins for normal young adults are listed in Table II. The suggested therapeutic dosages during an illness are listed in Table III. It is estimated that during a serious illness a young adult requires from three to ten times the amounts of the various vitamins required for maintenance during a period of good health. We have assumed that during the first two or three days of an acute and serious illness in an elderly patient, three times the therapeutic dose of these vitamins should be administered

each day and, in addition, one gram of vitamin C is indicated. Thereafter, two therapeutic doses and up to one gram of vitamin C is administered daily during the illness and the

TABLE III
A Formula for Standard Vitamin Therapy*

Thiamine HCl.....	10 mg
Riboflavin	10 mg
Niacinamide	100 mg
Calcium Pantothenate.....	20 mg
Pyridoxine HCl.....	2 mg
Folic Acid.....	1.5 mg
Ascorbic Acid.....	300 mg
Vitamin B ₁₂	4 μ g

* From "Therapeutic Nutrition," National Academy of Sciences—National Research Council, Publication 234.

convalescent period. The vitamins are administered orally except when there is evidence to indicate poor gastrointestinal function. When the oral route is not used they are added to 1000 to 1500 ml of intravenous fluid, or are administered by the intramuscular or subcutaneous routes. They should not be administered undiluted intravenously because of the high rate of excretion following intravenous injection in a short period of time. It has been suggested that a young adult who has not had an adequate diet for more than 10 days, or who has an illness expected to last more than 10 days, should receive supplementary vitamins.⁴

Riboflavin, nicotinic acid, pantothenic acid, and pyridoxine are necessary for protein metabolism when protein is utilized for the repair and replacement of body proteins. A deficiency of one or more of these vitamins may prevent adequate protein utilization. A deficiency of riboflavin, like a deficiency of ascorbic acid, will retard wound healing. A nicotinic acid deficiency will embarrass protein utilization long before the clinical signs and symptoms of pellagra appear. Riboflavin is required for the oxidative processes of the body. Nicotinic acid, like thiamine, is necessary for adequate carbohydrate metabolism. Pantothenic acid acts as a coenzyme in enzymatic acetylation. It also appears to be involved in adrenal function, and under experi-

mental conditions pantothenic acid depletion may lead to adrenal cortical exhaustion. Pantothenic acid is involved in antibody production, the decarboxylating and reaminating reactions involving various amino acids. It also has some neutral fat-sparing action. Folic acid is a hematopoietic and a leukopoietic. It therefore helps to maintain the red blood cell mass and the development of leukocytes—one of the body's defense mechanisms against infections. Vitamin B₁₂ is the potent antianemic substance of the liver. It also seems to have an important function in the transmethylation process and may facilitate utilization of marginal intakes of protein.

It is well to remember that (1) the clinical avitaminoses are rare; (2) the subclinical deficiencies are common, especially in the aged; (3) the subclinical deficiencies have multiple and profound influences on the physiologic processes of the body; and (4) for optimum therapy the physician must assume that all ill elderly patients are deficient.

Hydration

The degree of hydration is determined on the basis of the history, physical examination, and examination of the urine. Sunken eyes, dry tongue and mouth, excessive thirst, and urine with small volume and high specific gravity usually indicate a water loss equivalent to 6 per cent or more of the body weight. A loss of 15 per cent is usually incompatible with life.⁴ Inadequate sodium intake may prevent the retention of water. Excessive amounts of sodium and/or hypoproteinemia may lead to the production of edema when attempts are made to hydrate the patient. Rehydration should be approached cautiously in the elderly patient. When the clinical symptoms of dehydration are present and the patient is unable to take fluids by mouth, 6 per cent of the body weight of fluid is administered intravenously, in addition to the daily requirement of fluid over a period of three to five days. Fluid balance is restored as other deficiencies are corrected. A 150-pound patient with the clinical signs and symptoms of dehydration would have a deficiency of at least 9 pounds, or roughly 4500 ml of water. If this were to be

corrected in five days, then 900 ml of fluid should be added to the daily requirement of 2000 to 2500 ml of fluid per 24 hours. If other deficiencies are corrected and if hydration is then not complete, one must assume that the dehydration amounted to more than 6 per cent and additional supplementary amounts of fluid should be administered during the next few days. Blood chemical determinations, as previously mentioned, should be repeated every second day because deficiencies which could not be determined when the patient was first seen may become apparent as hydration is established. Adequate hydration of an adult is usually achieved when the patient is improved clinically, the blood chemical values approach normal, and the daily urine volume approaches 1000 ml. In the presence of renal damage, a urine volume of as much as 1500 ml is occasionally required to excrete the daily amount of urinary solids.

Electrolyte Deficiencies

When an electrolyte disturbance is suspected, serum sodium, potassium, chloride, and CO₂ determinations should be done. If a serious deficiency exists, these determinations should be repeated every second day and more often, if necessary, until the abnormality is corrected or the patient has recovered clinically. It should be clear, however, that the patient should be treated mainly on the basis of the clinical findings and not entirely on the basis of chemical determinations.

Sodium depletion can frequently be diagnosed on the basis of weakness, lassitude, headache, giddiness, muscular cramps, and weight (fluid) loss. The usual daily allowance of sodium chloride is 6 g, the amount contained in approximately 700 ml of physiologic sodium chloride solution. The excess chloride is usually excreted by the kidney but occasionally it is retained in the presence of renal damage. When there is known renal damage it is best to administer sodium as a mixture of 2 parts physiologic saline to 1 part of 1/6 molar sodium lactate, in order to provide an adequate amount of sodium without at the same time providing an excess of chloride.

Although chemical formulae should not be

used to correct mineral deficiencies, they are occasionally useful in estimating the total dosage which might be required. A satisfactory formula for chloride replacement is as follows:

$$100 - (\text{observed mEq of Cl}) \times (\text{wt in kg}) \times 29.3 = \text{milliequivalents of sodium chloride required}$$

A more accurate estimation can be made on the basis of the measured body thiocyanate space; however, thiocyanate space determinations are seldom done by the ordinary hospital laboratory.

Deep and exaggerated respirations are usually indicative of acidosis. Shallow and irregular respirations with muscular hypertonicity and hyperactive reflexes suggest alkalosis. Urinary pH is not necessarily a satisfactory index of the existence of alkalosis or acidosis. A urinary tract infection, for instance, may produce an alkaline urine even though the patient is in acidosis. Occasionally, an elevated CO_2 combining power value will be the result of long-standing acidosis and not the result of alkalosis as one ordinarily would assume. The determination of the pH of the blood is the last court of appeal and is the only absolutely reliable means of determining whether or not acidosis or alkalosis exists.

Alkalosis is usually adequately treated with physiologic saline solution, provided there is no potassium deficiency and there is normal renal function. Occasionally, it is necessary to use a 2 per cent ammonium chloride solution to treat alkalosis. One gram of ammonium chloride will reduce the CO_2 value one volume per cent (0.045 mEq) in an 150-pound adult.⁹ Severe acidosis which does not respond to adequate fluid and sodium chloride therapy should be treated with sodium lactate. Hartmann's formula (which follows) is used to calculate the amount required:

$$0.3 \times (\text{wt in kg}) \times (60 - \text{observed } \text{CO}_2 \text{ in volume } \%) = \text{ml of molar lactate required}$$

The required amount of molar lactate solution is then diluted with 5 parts of water or other intravenous solution to form a 1/6 molar lactate solution. Elderly patients will tolerate the calculated dose if administered over a

number of hours, provided the total amount of fluid is not excessive for the aging cardiovascular system.

Potassium deficits occur from trauma, hemorrhage, diabetic ketosis, vomiting, diarrhea, or the administration of excessive amounts of corticotropin (ACTH), or cortisone. A hypochloremic alkalosis almost always indicates a potassium deficiency. Potassium is administered in the form of potassium chloride, 2.23 g per liter of intravenous fluid, which is equivalent to 30 mEq of potassium mineral per liter of fluid. Potassium is never administered during the first two postoperative days. When intravenous fluids have been the only form of alimentation for more than two days, 30 mEq of potassium should be provided each day. When vomiting or other abnormal losses of body fluids have continued for more than two days, additional amounts of potassium equivalent to the calculated losses should be administered.

Administration of potassium in the presence of renal damage, may lead to arrhythmia or arrest because of retention of potassium and the production of hyperpotassemia, and hyperexcitability of the heart. Never, or almost never, administer intravenous potassium in the presence of renal damage. For severe deficiencies, up to 60 mEq and occasionally 120 mEq may be administered in a day. At least one hour should be allowed for administering 30 mEq of potassium.

NUTRITION DURING AND AFTER OPERATION

As previously noted, during operation and the first postoperative day no sodium chloride solution is administered to the patient except the small amounts necessary to start blood transfusions and the amounts calculated to replace sodium losses which have occurred or continue to occur as the result of loss of gastrointestinal fluids, diarrhea, fistula drainage, etc. For the more extensive operations a continuous drip of a 5 per cent glucose in water solution is used to replace fluids lost by perspiration and exudation. Blood losses of more than several hundred ml are replaced with equivalent amounts of whole blood. In the absence of abnormal losses of body fluids

which contain sodium, sodium is withheld for 48 hours because following the trauma of operation this electrolyte (like water) is retained in the body. When oral intake is not possible in the postoperative period, from 2500 to 3000 ml of fluid, usually in the form of 5 per cent glucose in water, is administered. Multiple-vitamin preparations are included in the intravenous fluids and continued by mouth when oral alimentation is possible. Suggested dosages are given in the discussion on preoperative vitamin requirements. Because 1500 ml of 5 per cent glucose and 1000 ml of 5 per cent protein hydrolysate or "amino acid solution" will provide only 850 calories per day, and because in the absence of abnormal body fluid losses the hydrated elderly patient usually cannot take more than 3 liters of fluid a day, it is useless to give the protein hydrolysate. One might just as well give an additional liter of 5 per cent glucose solution instead, because it will provide practically the same number of calories, 800 calories, and it is more easily metabolized. When intravenous fat emulsions are safe enough for general use, perhaps a sufficient number of calories can be provided so that protein hydrolysates can be used for restoration and repair of tissue. Intravenous alcohol cannot safely be given in sufficient amount to spare the protein in the hydrolysates from being used for energy requirements.

For the replacement of abnormal loss of body fluids, a solution consisting of half 5 per cent glucose in water and half physiologic saline is given in amounts equal to the measured or estimated abnormal loss. The urinary output need not exceed 500 to 570 ml on the day of operation and the first postoperative day, because of the retention of fluid (and sodium) during the first 48 hours after surgical trauma. Thereafter, the urinary output should be from 800 to 1000 ml per day. If renal function—concentration power—is diminished, as much as 1500 ml of urine per day may be necessary. Potassium is never administered until the third postoperative day, and then only if oral alimentation is not possible. If on the third postoperative day it appears that the patient will not be able to take any alimentation by mouth, then 2.23 g of

potassium chloride (30 milliequivalents of potassium) should be added to the intravenous solutions daily. If there is excessive loss of body fluids (exclusive of urine), larger amounts are indicated. No intravenous potassium therapy is used in the presence of renal damage, or it is used with extreme caution in special cases! Prolonged intravenous therapy and abnormal loss of body fluids call for sodium, potassium, chloride, and CO_2 determinations every second or third day.

The transition from intravenous fluids to "liquid," "soft," and "regular" hospital diets is made as rapidly as the patient's condition permits. A hungry patient is usually a patient making satisfactory progress, and by all means he should be allowed to make that progress nutritionally. It is a well-established fact that following operations ranging from herniorrhaphy to subtotal gastrectomy patients lose from 2.5 to 23 pounds during the postoperative period.¹⁰ It is the surgeon's duty to the patient to minimize the weight loss, of course, without jeopardizing the patient's condition. In present-day surgical practice, one should *never* routinely order "nothing by mouth for two days postoperatively, liquids for two days, soft diet for two days, and a regular hospital diet on the seventh postoperative day." If the surgeon is satisfied with his operative technique and if the patient's general condition is good and he is thirsty, give him something to drink. If he manages fluids well for 6 or 8 hours and is hungry, prescribe a soft diet. If he manages this well for 6 or 8 hours and wants an additional amount of food, order a regular diet. Frequently even patients with gastric, small intestine, or colon resection will be benefited by adequate amounts of food early in the postoperative period. Often when the surgeon is completely satisfied with the intestinal anastomosis, peristaltic sounds are present, the abdomen is soft and flat, the patient's condition is good, and the patient is hungry, the long or short suction drainage tube can be removed and the patient can be given water, 30 ml per hour, on the morning of the second postoperative day. If his condition is satisfactory after 6 or 8 hours, he can have a liquid diet.

Shock

Although shock is not usually included in discussions of nutrition, the fact that hypovolemia and protein deficiency are more prevalent in the older patient than in the younger patient makes such a discussion important. It is all the more important because the elderly patient has diminished functional reserves, which embarrasses his possible recovery from shock. The most frequent cause of shock following operative or accidental trauma is blood loss. Infection, if not extensive and established at the time of operation, is rarely the cause of shock during the first and second postoperative day. Cranial trauma rarely produces shock.¹¹ Respiratory obstruction, cardiac tamponade, and heart failure, among other things, can produce shock with little or no loss of blood; however, these situations should be obvious to the alert surgeon after a brief history and physical examination. The neurogenic syndrome or the vasovagal reaction does not produce shock if the criteria of shock are (1) a pulse over 100, (2) blood pressure of less than 100 mm Hg, (3) cool skin of extremities, and (4) pale skin of the face. When the history and the physical examination give no evidence of the afore-mentioned rather infrequent causes of operative shock, and when these four signs and symptoms are present, one can be quite sure that the patient has lost or is deficient in more than 30 per cent of his normal expected blood volume.¹² Malnutrition or, more specifically, a protein deficiency, may have reduced blood volume to a seriously low level. Minor trauma of operation and anesthesia and minor blood loss may then produce shock. The important thing to remember in the treatment of shock is that with a blood volume deficit the elderly patient needs just as large an amount of whole blood, administered just as rapidly, as does a young adult. When the signs and symptoms of shock have disappeared, do not forget that the patient is probably still deficient in 20 to 30 per cent of his expected normal blood volume. This amount can be replaced, if necessary, in order to prepare the patient for further elective surgery, but this portion of

the blood replacement must be accomplished slowly because of the limited reserve of the cardiovascular and pulmonary systems of the aged patient. Once shock no longer exists, replacement of blood probably should not be more rapid than 500 ml administered over a two- or three-hour period each day until the blood volume is slightly less than normal or the hematocrit approaches 50 per cent, or the hemoglobin approaches 100 per cent.

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Editorial

The Structure of Vitamin B₁₂

Announcement was recently made of the establishment of the structure of vitamin B₁₂. Two teams of investigators, a group at Oxford¹ (with an assist from U.C.L.A. and Princeton) and a group at Cambridge² both report the identical structure in the same issue of *Nature*. The former group based their studies largely on crystallography, whereas the latter emphasized biochemical reactions.

The complex structure has the formula C₆₃H₉₀O₁₄N₁₄PCo, and the configuration of the molecule is illustrated in the reports. Nutritional chemists may well be proud of this bilateral achievement, coming a short seven years after the isolation of this remarkably potent substance. To E. Lester Smith of the Glaxo Laboratories in England goes the distinction of being one of the two original isolators of vitamin B₁₂, and also one of a

group which has now defined its structure.² Nor should it go unnoticed that, as in the case of its isolation, the establishment of the structure of vitamin B₁₂ was achieved simultaneously by two groups working independently—a form of scientific competition which can only lead to greater advances at a more rapid pace.

—S. O. WAIFE, M.D.

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Vitamins—Foods or Drugs

From time to time the Food and Drug Administration is asked if vitamins are foods or drugs. As defined in the Food, Drug, and Cosmetic Act, the term "food" means (1) articles used for food or drink for man or other animals; (2) chewing gum; and (3) articles used for components of any such article. The term "drug" means (1) articles recognized in the official U. S. Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other

animals; and (3) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (4) articles intended for use as a component of any articles specified in clause (1), (2), or (3); but does not include devices or their components, parts, or accessories.

These definitions do not classify vitamin preparations in one category or the other. Vitamins are, in fact, included in both, and the courts have held that the food sections of the Law and the drug sections are not mutually exclusive. If a product is found to be in violation of the Act, then the intended use

of the product determines whether the food chapter or the drug chapter is applicable. The intended use will determine whether there has been a violation of the food or drug section. The label may be important in determining intended use, but equally important are the oral representations of salesmen to purchasers, oral or written instructions or suggestions of salesmen, and the relaying of these instructions to the physician or retailer. Newspaper, radio, or television advertising are also factors in determining intended use.

Notwithstanding the innocuous labeling of the drug itself, the dosage form may, in some cases, be significant in this determination. An encapsulated vitamin in a therapeutic dose with or without the additional factors mentioned above may, in some cases, be enough to tip the scales in favor of a drug determination. Intent for use for the cure, mitigation, treatment or prevention of disease makes a preparation subject to the drug chapter of the Act. Preparations properly labeled to indicate that they are for the physician's use for the treatment of disease or injectable preparations obviously must be regarded as drugs. A product offered as a food supplement and supplying a vitamin or vitamins in amounts not greater than intended to meet daily needs is a "food for special dietary use," and not a drug.

But, you say, articles listed in the U. S. Pharmacopeia are drugs and there are about a dozen vitamin products in the U. S. Pharmacopeia. Even though the law recognizes articles in the U. S. Pharmacopeia as drugs, an exception is made in the case of foods for special dietary use, and this exception must be recognized. From the above it should be clear that there is no simple classification of vitamin preparations either as foods or drugs.

If we use Webster's International Dictionary as a guide, we come to the conclusion that vitamins may be regarded as foods when used as foods, and as medicines when they are used for that purpose. Food is defined as "nutritive material absorbed or taken into the body of an organism which serves for purposes of growth, work, or repair, and for the maintenance of vital processes." A drug is "any sub-

stance used as a medicine or in making medicines for internal or external use," and medicine is defined as "any substance or preparation used in treating disease." Preparations offered in amounts that will serve to supply the maintenance requirements of the body with respect to nutrition and not intended for use or offered for use other than as food supplements should therefore be regarded as foods.

Since a food serves the purpose of providing the needs for growth, work and maintenance, and life cannot be maintained in the absence of vitamins, we must regard vitamins as food. However, when administered in suitable amounts, a vitamin may bring about the disappearance of symptoms of serious disease and restore health. The vitamin is then serving the function of a medicine.

This classification does not satisfy those who consider as medicines pills and capsules or solutions to be taken by the drop or teaspoonful. These are the forms in which drugs are usually administered, and are indicative of items obtained from a drug store. Fifty years ago this would have been a valid position, but scientific developments have brought forth some new facts that call for further consideration.

The dual role of vitamins as foods and drugs no doubt stems from the small quantities needed to perform a useful function and the ease with which potent pharmaceutical preparations can be manufactured. We express ourselves in milligrams and micrograms in speaking of a day's requirement of the vitamins and trace minerals, and in grams and kilograms in expressing the quantity of food that will supply the day's need for proteins and energy-yielding food. Congress recognized this unique position of the vitamins and minerals in a special section of the Food, Drug, and Cosmetic Act, and provided for labeling requirements for foods "for special dietary use" represented to have "vitamin, mineral, or other dietary properties."

A vitamin performs an inherent function that cannot be performed by anything else, and it does not promote science to try to define that function as one characteristic of foods or of drugs. There are legal situations

in which such a definition is required. For this purpose *the intended use* is the best basis for such differentiation. In those instances where it becomes important or necessary to reach a decision with respect to the kind of products that should be considered as drugs or foods (such as for control of representations or for tax purposes), the authority for such

purpose could so define the subject to be covered that no controversy should arise.

—E. M. NELSON, PH.D.

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Letter to the Editor

PERSONAL EXPERIENCE WITH PAROTID ENLARGEMENT

Dear Sir:

The report of Sandstead, Koehn, and Sesoms regarding enlargement of the parotid gland in malnutrition (AM. J. CLIN. NUTRITION 3: 198, 1955) suggested that some details concerning my personal experience with this disorder may be of interest. Various results of Dr. A. J. Carlson's experiments on my food restriction and fasting were previously described,^{1,2,3} but the development of parotid enlargement was not mentioned. In brief, "asymptomatic" bilateral parotid enlargement began to develop in 1908 when I ate freely after a period of about six months during which I restricted my food intake and, particularly, my protein intake.

The value of protein restriction at that time seemed to be supported by the findings in the studies made by Chittenden.⁴ Although no evidence of parotid enlargement was noted while my total calorie intake was considerably restricted (the food I ate consisted largely of fruit and sugar), I found evidence of excessive water retention.^{2,3} At that time this was assumed to indicate "autointoxication," but between 1917 and 1919 it became evident that the water retention was nutritional edema promoted by semistarvation, and particularly by protein starvation, with the inclusion of some salt in my diet. My food intake was increased in 1908, largely through the addition of potatoes, bread, and cabbage (sauerkraut). This,

incidentally, increased the salt intake considerably and a rapid increase in nutritional edema occurred. My entire body seemed to swell or become bloated and the swelling in the parotid region merely seemed to be the most prominent evidence of this general swelling. I looked as if I had the mumps but the swelling on the right side was somewhat greater than on the left. I also became mentally and physically very sluggish and this suggested in 1909 that I was afflicted with myxedema.

As the increase in my food intake appeared to be responsible for the generalized swelling or assumed increase in autointoxication, I restricted my food intake again and more drastically than before. I believed that fasting would serve best to reduce the swelling, but at that time fasting seemed to be too great an ordeal to be practical. Hence, I tried eating only enough citrus fruit to mitigate hunger. During 17 days in which I ate only oranges and a few lemons, the generalized as well as the local (parotid) swelling disappeared almost completely. Incidentally, I also became more alert mentally.

As a result of a fall I came under the care of a physician who prescribed a liberal diet "with plenty of vegetables like turnips." The generalized and mumps-like swelling consequently became greater than before within

about two weeks. When I complained that the vegetables appeared to be mainly responsible for the disfiguring parotid swelling, this physician said that the swollen glands, which were then assumed to be swollen parotid lymph nodes, could be removed surgically but that vegetables were needed in my diet. After this physician's attention to my injury was no longer needed I stopped eating the seemingly harmful vegetables and made bananas the mainstay of my diet, and my general condition improved. Obviously, the salt added to the vegetables was mainly responsible for their apparent harmful effect.

Details concerning my further experience before 1917 need hardly be presented here except to say that it involved repeated flare-ups in generalized edema and parotid enlargement whenever I did not, or could not, adhere to a fruitarian diet; improvement occurred when I adhered to such a diet or fasted. The most rapid improvement occurred during short fasts and this led me to try a prolonged fast in the hope of obtaining complete relief. A great general improvement was produced by a 26-day fast in 1913 but more fasting seemed to be needed within a year. Photographs of me that were taken in 1917 before and after 15 days of fasting at the University of Chicago, and which were included in Dr. Carlson's report of the study of hunger that he then made on me,¹ clearly show enlargement of the parotid on the right side or a swollen condition of the entire right side of my face before fasting and a more nearly normal appearance at the end of the fast. I do not know when the parotid swelling on the less affected left side disappeared or whether a slight residual enlargement still exists. The difference in improvement here appears to be similar to what I have noticed in regard to the effect of fasting on local fat deposits. The subcutaneous fat seems to disappear fastest or most completely in areas where the least excess exists. Moderately enlarged parotids are evidently often assumed to be normal.

The importance of salt as a factor explaining the flare-up of nutritional edema and enlargement of the parotids after fasting or a period of food restriction was discovered dur-

ing the study made at the University of Chicago in 1917.¹ The value of a liberal protein intake in preventing or limiting the salt-water edema was discovered in our experience in 1918 and 1919. However, the enlargement of my right parotid region or entire right side of my face evidently became chronic or involved some irreversible changes already before 1913 and no significant improvement was produced by fasting even as long as 41 days (in 1925) and using diets high in protein.

As reported by others, one may not experience any discomfort with such parotid enlargement. Only a slight sense of tension in the parotid region was experienced when my parotids were most swollen—in 1909 and 1910. I did not realize how asymmetric my facial appearance remained after 1910 until this was revealed by photographs. A mirror revealed that the mobility of the right side of my face had also become impaired so that I tended to smile only on the left side and the impression I made on others seemed to depend on which side of my face they saw or whether they noted the asymmetry. I did not note any other disturbance until about 1942 when I began to wear glasses. It then became evident that the skin around my right ear was hypersensitive to the slight pressure or pinching occasioned by wearing glasses. It is still necessary to change their position from time to time for relief. About two years ago (1953), I became more concerned about the possible complications, because I began to be troubled with earache on the right side. A further enlargement of the parotid gland did not appear to be responsible for the trouble, although the gland appears to be becoming firmer to palpation. In any case, the earache led me to give my nutritional state closer attention and the earache disappeared with a regimen whereby I got rid of some fat and apparently also some excess fluid ("subclinical" edema).

I was aware long ago that it was much more difficult to get good results in shaving around my right jaw than around my left jaw. This has evidently been due to a poorer skin tone or edematous condition of the skin around the somewhat enlarged submaxillary salivary gland on the right side. This was previously

also thought to be an enlarged lymph node. Sensitiveness to the pull of a somewhat dull razor has served about as well as the palpable size of my right parotid salivary gland as an index of excessive hydration. Some unexplainable variations have been noted to occur from time to time within a few hours but seem most likely to be due to variations in the absorption of products of digestion and fluid from the digestive tract.

In my opinion, only observations of the conditions under which parotid enlargement begins can shed light on this disorder. Fatty infiltration or lipodystrophy⁵ and other changes evidently occur as a result of a more or less chronic edematous state.

Why the parotid salivary glands should become particularly enlarged in some individuals living on diets promoting the development of nutritional edema remains a question. However, the finding of Fawcett and Kirkwood⁶ that salivary glands have a "reverse thyroid" function suggests that they may play a specific role in nutritional edema. I suspect that an iodine deficiency as well as protein deficiency may explain severe nutritional edema. Incidentally, this would link nutritional edema with myxedema.

In any case, parotid enlargement needs closer attention. I have been surprised by the general indifference of physicians to my parotid swelling, even when it was pointed out to them. Sandstead and his associates refer only

to bilateral enlargement but Kenawy⁷ found unilateral enlargement in 18 of 100 cases. Symmetric bilateral enlargement is evidently most common and unilateral enlargement may merely be the result of a failure of acute bilateral enlargement to disappear on one side. The effect of parotid enlargement on neighboring tissues will best be revealed in cases of unilateral enlargement.

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Nutrition News

News of activities in the field of clinical nutrition should be submitted to the Editorial Office of the JOURNAL.

American Board of Nutrition

The American Board of Nutrition will hold the next examinations for certification as a Specialist in Human Nutrition in April 1956. Applications for certification should be in the offices of the Secretary not later than February 1, 1956. Application forms may be obtained, on request, from the Secretary, Otto A. Bessey, Department of Biochemistry and Nutrition, The University of Texas School of Medicine, Galveston, Texas.

Borden Nutrition Award

Dr. L. Emmett Holt, Jr., was the recipient of the annual Borden Nutrition Award, bestowed on him on October 5, at the American Academy of Pediatrics convention in Chicago.

Dr. Holt is Professor and Chairman of the Department of Pediatrics of the New York University College of Medicine and one of the leading authorities on pediatrics in this country. This most recent honor goes to him "in recognition of his many contributions, during recent years, to the field of infant nutrition regulations for essential amino acids his careful determinations of the minimal nutrition regulations for essential amino acids and vitamins."

Conference on Nutrition in Disease

Under the co-chairmanship of Drs. Michael G. Wohl and Robert S. Goodhart, a *Conference on Nutritional and Metabolic Considerations in Disease* was held at the College of Physicians, Philadelphia, on November 9. Sponsors of the Conference were The Commission on Nutrition of the Medical Society of the State of Pennsylvania and the Philadelphia County Medical Society, and the National Vitamin Foundation.

Dr. W. H. Sebrell, Jr., addressed the banquet guests on "The Increasing Importance of Nutrition in the Practice of Medicine and

Public Health." Among the speakers and discussers were: Drs. Norman Jolliffe; Irvine H. Page; Douglas Gordon Campbell; I. S. Ravdin and R. G. Ravdin; Garfield G. Duncan; John H. Browe; Campbell Moses; Peter T. Kuo; Ivan F. Bennett; and William T. Fitts, Jr.

Diabetes Day

On October 27, the Clinical Society of the New York Diabetes Association presented its third Symposium Day on Diabetes Mellitus, devoted to the consideration of *The Pituitary-Adrenal System and Diabetes Mellitus*, with Dr. Henry E. Marks, Association President, presiding, and a number of distinguished speakers.

Vitamin Symposium

The Role of Some of the Newer Vitamins in Human Metabolism was the subject of a symposium held at Vanderbilt University, Nashville, Tenn., October 21-22.

Dr. William J. Darby, Director of the Division of Nutrition, Departments of Medicine and Biochemistry, Vanderbilt University, directed the symposium, the twelfth in a semi-annual series sponsored by the National Vitamin Foundation. Dr. Darby, Drs. Amos Christie, Paul György, and Hugh Morgan served as Chairmen of the several meetings, and the following outstanding speakers were heard: Drs. Paul György; James F. Rinehart and Louis Greenberg; Maurice Victor and Raymond Adams; David Coursin; E. W. McHenry; M. Wachstein; Richard Vilter; Paul L. Day and James Dinning; Harry Gordon; Philip L. Harris; M. K. Horwitt, C. C. Harvey, G. D. Duncan, and W. C. Wilson; and William Bean. Discussers were Drs. Gladys Emerson, Norman Olson, Charles May, W. J. McGanity, Henry Sebrell, Grace Goldsmith, Beverly Towery, and Floyd Daft.

Nutrition Briefs

CURRENT OBSERVATIONS OF CLINICAL INTEREST

No DIFFERENCE in rate of weight loss was found between persons on high fat, low carbohydrate diet compared to an isocaloric low fat, high carbohydrate diet.

S. C. Werner. *New England J. Med.* 252: 661, 1955.

POSTPRANDIAL lipemia after a high fat meal may provoke anginal symptoms in patients with coronary artery disease. These effects occurred about five hours after eating (at the peak of the hyperlipemia) and not shortly after a meal when increased cardiac work may be a factor.

P. T. Kuo and C. R. Joyner, Jr. *J. A. M. A.* 158: 1008, 1955.

ANIMAL and plant proteins had an equal effect on the blood sugar when given for breakfast to diabetic subjects.

J. Zickefoose, R. C. Hardin, W. W. Tuttle, K. Daum, and J. Salzano. *J. Am. Dietet. A.* 31: 1016, 1955.

DIABETES in plethoric adults, or diabetes due to "adipose encumbrance," is cured in a great number of cases by weight-reducing treatment. The more recent the diabetes, the more certain is the cure.

Ch. Darnaud. *Sem. Hôp. Paris* 21: 1073, 1953.

NAVY RECRUITS on antibiotic prophylaxis for 7 weeks gained more weight than a comparable placebo group. This is significant in view of growth effects of antibiotics in livestock.

T. H. Haight and W. E. Pierce. *J. Nutrition* 56: 151, 1955.

FAT CONTAINED in stable emulsions is largely removed from the circulation within 3 or 4 hours after intravenous injection. The rate of removal and distribution are influenced by systemic factors as well as characteristics of the emulsion itself.

S. Freeman. *Progress Chem. Fat and Other Lipids* 3: 2, 1955.

THE CAFFEINE content per cup prepared from regular ground coffee bean is roughly three times

that of regular "decaffeinated" coffee and from four to eight times that of instant decaffeinated coffee.

J. A. M. A. 158: 1030, 1955.

A PREVIOUSLY undescribed amino acid has been isolated by chromatography. It occurs in small quantities in the peel, but not the pulp, of certain apples. It is thought that it may be a methyl-hydroxyl-proline.

A. C. Hulme. *Nature* 174: 1055, 1955.

RECENT ADVANCES IN EXPERIMENTAL NUTRITION

AUREOMYCIN increased both the degree of calcification and weight gain of rats on a rachitogenic diet and graded doses of vitamin D; by itself the antibiotic had no effect on calcification or weight gain.

T. K. Murray and J. A. Campbell. *Canad. J. Biochem. & Physiol.* 33: 797, 1955.

MICE WITH the hereditary obese-hyperglycemic syndrome and alloxan diabetic mice survived significantly longer than controls after intraperitoneal injection of Ehrlich mouse ascites carcinoma cells.

J. Jehl, J. Mayer, and R. W. McKee. *Cancer Res.* 15: 341, 1955.

VITAMIN B₁₂ increased the impairment of growth brought about by pantothenic acid deficiency in birds. Increased B₁₂ intake resulted in increased B₁₂ content of the liver. Addition of pantothenic acid to the diet augmented this effect. A high intake of pantothenic acid was required to increase the content of liver pantothenic acid.

B. E. Welch and J. R. Crouch. *Proc. Soc. Exper. Biol. & Med.* 87: 121, 1954.

CRYSTALLINE insulin has been labeled by direct iodination with I¹³¹. Studies on the distribution of protein-bound iodine¹³¹ show that continuous infusions give higher blood and tissue levels than the same dose in a single intravenous injection.

S. Rose and Y. Nelson. *Australian J. Exper. Biol. & Med. Sc.* 32: 429, 1954.

SEXUAL maturity is delayed by vitamin B₁₂ deficiency in female rats whose mothers were fed a vitamin B₁₂-deficient ration during lactation. Changes in the nature of carbohydrate and protein in the ration resulted in variation of response to vitamin B₁₂ deficiency.

L. P. Dryden, A. M. Hartman, and C. A. Cary. *Proc. Soc. Exper. Biol. & Med.* 87: 195, 1954.

Reviews of Recent Books

Vitamins in Theory and Practice (fourth edition), by Leslie J. Harris, Cambridge University Press, 1955, pp. 366, \$6.50.

This is a thoroughly delightful book. What is more, it manages to be highly entertaining while remaining "scientific." Physicians who are wont to scorn any piece of writing which is not exclusively intelligible to members of their profession (and one sometimes wonders if even . . .) will be utterly disarmed by Dr. Harris.

As for the "common reader," the author neither discourages his curiosity by overburdening him with minutiae, nor encourages his complacency by oversimplification. The boy who said in a book review that the volume told him "more than he wanted to know" about its subject would have no reason to complain of this succinct but thorough presentation of a fascinating topic. For here, copiously illustrated, is "what everyone should know" about the vitamins: how they were discovered, who unravelled their mysteries, what they do in the body, what happens when they are not supplied. The whole exciting story of vitamin research and the gradual conquering of deficiency diseases is laid before the reader, and the "morals" are drawn in terms he can apply to his own nutritional habits.

Let physicians and patients alike make haste to lay hands on this lively volume. And let tired biochemists, pondering their structural formulae, look to Dr. Harris and find themselves more glamorous than they thought.

C. J. H.

Diseases of the Liver and Biliary System, by Sheila Sherlock, Charles C Thomas, Springfield, Ill., 1955, pp. 720, \$10.00.

The liver is the central organ of metabolic functions. It is situated athwart between the intestinal tract and the "internal milieu" of the organism and, as such, it is and must be greatly influenced by nutritional factors. The present book is "a comprehensive and up-to-date account of diseases of the liver and biliary system," written mainly for "physicians, surgeons and pathologists and also as a reference book for the clinical student." Its author, Sheila Sherlock, is one of the foremost students of the liver, with a wide clinical knowledge and outstanding originality in studying the many aspects of the pathology and function of the liver and its accessory organs. Sherlock points out the dietary implications in the many physiologic and

pathologic functions of the liver with great understanding and proper clinical appraisal. The most recent observations of the author's group on the deleterious effect of high protein intake in decompensated liver are of especial interest and in full accord with similar observations of C. S. Davidson and his associates at the Boston City Hospital.

Dr. Sherlock's book belongs on the bookshelf of physicians, surgeons, nutritionists, and physiological chemists interested in the physiology and pathology of the liver. It will remain a standard book for many years.

P. GRÖGY

Nutrition for Practical Nurses, by Phyllis S. Howe, W. B. Saunders Company, Philadelphia and London, 1955, pp. 174, \$2.50.

Practical nurses are being given more and more responsibility for the bedside care of people who are ill in the hospitals and in the homes of our nation. It is often the duty of the practical nurse to prepare, serve, and feed a nutritious and suitable diet to her patient. For good patient care, this nurse needs to be convinced that good diet is a necessity for recovery from illness. She must know how to provide the essential nutrients in attractive meals that will be tempting to even the poorest appetites. As a reference for the practical nurses and a guide for their teachers we have needed a simple nutrition manual written especially for this group. In this book, the author attempts to provide such a textbook. Unfortunately, she does not relate the theoretical material presented to the work of the practical nurse.

The practical nurse who reads this book will learn to pronounce and define many of the technical terms used by dietitians. She will be exposed to a smattering of an oversimplified version of the chemistry and physiology of normal nutrition, the medical basis of a very few therapeutic diets, and the scientific principles concerning the selection, preparation, and care of basic food products.

Practical nurses might use this book to cram for State Board Examinations. They will neither enjoy reading it, nor will it stimulate them to prepare more nutritious, attractive meals for the patients. It will do little to motivate them to improve their own eating patterns. Nutritionists and dietitians will question the accuracy of many of the statements and over-generalizations. They will be disturbed to find the "Basic Seven" presented as the one and only formula for planning adequate meals. Most of all, they will

regret that Miss Howe just missed supplying them with the readable, accurate, inspiring nutrition text that we need for our practical nurse students.

MILDRED KAUFMAN

The Low Sodium Cook Book, by A. S. Payne and D. Callahan, Little, Brown and Company, Boston, 1953, pp. 477, Bound, \$4.50; Paper (Sunkist Growers Spec. Ed.), \$1.25.

This book, as its title implies, is primarily a cook book, but it contains much other information as well for the person who must be on a restricted-sodium diet. In addition to tables presenting the sodium, cholesterol, and fat content of various foods, and sources of supply of dietetic foods, there is a discussion of the principle of the restricted-sodium diet. Suggestions for carrying out such a diet in the home are given in considerable detail.

The book is written in a chatty manner directed to the patient himself. It is designed to be used in conjunction with a specific diet as prescribed by a physician. The material is authoritative and on the whole accurate, within the limits of our knowledge of the sodium content of foods at the time the book was prepared. It is questionable whether the accuracy implied by the calculation of the content of recipes to one decimal place for milligrams of sodium and grams of fat is warranted.

The average patient may find the form of the recipes and the detailed explanations given somewhat confusing and few patients would be able to use the book without the initial guidance of a dietitian. However, the patient who is above average in intelligence, with an interest in preparing attractive meals restricted in sodium, will find this cook book a welcome addition to his kitchen library. Physicians and dietitians should find material in this book helpful to the instruction of their patients.

DORIS JOHNSON

Yearbook of Endocrinology, edited by G. S. Gordon, The Year Book Publishers, Chicago, 1955, pp. 392, \$6.00.

The value of the Year Book Series for practitioners and clinical investigators is well exemplified by this volume on endocrinology. Not only is one provided with a ready reference for the significant contributions in this field and an adequate, practical summarization of the original article, but also there are excellent integrations and discussions throughout the volume. The relative merits of the reports contained in the volume are presented in the light of previous knowledge and related to current developments in the field. The interesting work of the editor and his associates supplies much of the material used in the evaluation of the abstracts. In the section on the adrenal gland, Drs. Leutcher and Curtis review the current status of aldosterone. This is followed by four articles on this subject. In another special article Dr. Bern-

stein deals with "Autotransplantation of Adrenal Cortex to Portal Circulation Combined with Adrenalectomy and Oophorectomy in Treatment of Metastatic Carcinoma of the Breast." The sections on adenohypophysis, thyroid, parathyroids and calcium metabolism, and carbohydrate metabolism detail the important advances in these aspects of endocrinology. The nutritionist will find this volume useful because of the references to the metabolism of foods, minerals, and substrates in relation to the endocrines.

C. R. SHUMAN

1955 Medical Progress, edited by M. Fishbein, The Blakiston Division, McGraw-Hill Book Co., Inc., New York, 1955, pp. 364, \$5.00.

This is the third volume of a series which present a yearly compendium of advances in medicine and surgery prepared by prominent teachers and physicians in their respective branches. The 1955 edition contains 20 chapters on a wide variety of topics, including many of the medical subspecialties. A chapter on nutrition by Shull, Davis, and Stare of the Harvard School of Public Health will be helpful in orienting the practitioner in the status of recent work in this aspect of medicine and surgery. Nutrition is referred to as "the single most important environmental factor affecting health" and is discussed in relation to atherosclerosis, coronary artery disease, and dental caries. Intravenous fat therapy, fructose in diabetes mellitus, and the roles of molybdenum, pyridoxine, and pantothenic acid are also reviewed in this section, which is limited in scope to the principal interests of its authors. Brief references are made to nutritional and dietetic factors in certain other chapters such as those dealing with liver disease, gout, and diabetes. The usefulness of the book is only slightly limited by the inability of several contributors to present a broad coverage of their respective fields; in general, most topics are admirably and succinctly surveyed.

C. R. SHUMAN

The Foreseeable Future, by Sir George Thomson, Cambridge University Press, 1955, pp. 166, \$2.50.

It is interesting to see how large a part this physicist assigns to biology in his "foreseeable future." Perhaps this is because further sophistication will have to depend on understanding and applying the more subtle processes of living organisms; these seem to involve "laws" as yet unknown and not reducible to the major principles of the universe by which physics and chemistry can be elucidated. Even if we cannot wholly understand the functions of living organisms, we can make use of them in new ways and, in some cases, imitate them. Thus Sir George sees the airplane wing becoming more flexible, "more like that of a bird," bridges, buildings, and other structures becoming "more like biological ones," biological methods of concentration—by sea-animals or plants—used to extract the rarer elements from sea-

water, climates altered by judicious planting, and so on.

Advance must always depend upon three factors: knowledge, energy, and materials. In the case of maintaining an adequate food supply for an increasing population, all three are involved. Biological research could develop better crops for potentially fertile tropical regions now sparsely inhabited. Ways could be found to freshen salt water for irrigation of deserts. Plants could be grown in water. The physical state of soils could be much improved by biologic or synthetic methods, preferably the former. Cheaper food, such as algae, could be grown for animal feeding, leaving more cereal foods for human consumption and increasing the supply of animal food. Even without new knowledge, there are possibilities for making better use of present resources. Why, asks Sir George, have we domesticated no new animals since the remote past? Why shouldn't monkeys be taught to pick fruit or other crops? And why do we limit ourselves to beef, mutton, and pork? "Surely some enterprising company or country should find it worth while to popularize antelope or bear."

Nobel Laureate for physics, the author lets us into his own field and invades ours with an impartial interest and intelligence rare in our age of specialization. Thus he considers the new (and older) sources of energy and power; methods of strengthening materials and developing new ones; the problems of communication and transportation (including, of course, space travel!); the prospects for weather and climate control; the possibilities of deliberate mutations; medicine's role in forestalling senility; the implications of computing machines; and the social changes we can anticipate in our altered world.

It is pleasant to report that Sir George's respect for living organisms extends to the human being, which, he says, "so vastly exceeds anything we are ever likely to be able to make." It is up to the human brain—and certainly not beyond its capacities—to insure that we shall actually see the future Sir George foresees so optimistically.

C.-J. H.

Books received for review by the *American Journal of Clinical Nutrition* are acknowledged in this column. As far as practicable, those of special interest are selected, as space permits, for a more extensive review.

Clinical Biochemistry (4th ed.), by A. Cantarow and M. Trumper, W. B. Saunders Co., Philadelphia, 1955, pp. 738, \$9.00.

Progress in the Chemistry of Fats and Other Lipids. Vol. 3, edited by R. T. Holman, W. O. Lundberg, and T. Malkin, Pergamon Press, London and New York, 1955, pp. 475, \$10.50.

Mental Hygiene in Public Health (2nd ed.), by P. V. Lemkau, McGraw-Hill Book Co., Inc., New York, 1955, pp. 486, \$8.00.

The Thyroid. A Fundamental and Clinical Text, edited by S. C. Warner, Hoeber-Harper, New York, pp. 789, \$20.00.

Vitamins and Hormones. Advances in Research and Application. Vol. XIII, edited by R. S. Harris, G. F. Marrian, and K. V. Thimann, Academic Press Inc., New York, 1955, pp. 382, \$9.00.

How to Reduce Surely and Safely, by H. Pollack with A. D. Morse, McGraw-Hill Book Co., Inc., New York, 1955, pp. 157, \$2.95.

Nationalistic Malnutrition

"The disadvantages of the food customs of impoverished Orientals have been emphasized in Western medical literature. The low-protein, low-caloric diet increases the spread of tuberculosis, decreases the resistance against most communicable diseases, favors the development of liver cirrhosis, transforms ankylostomiasis from a relatively harmless infestation to a dangerous disease. All this certainly clamors for correction and improvements. Nevertheless, the Oriental may also ponder the desirability of radical changes of the diet in the United States where, due to nutritional influences, so much gout, serious diabetes, obesity, gall stones, renal stones, amyloidosis, and premature coronary sclerosis occur. This might sound preposterous to our ears, but only because most people are adamant as far as their food preferences and aversions are concerned. No nation is willing to concede that its national diet may be lacking in certain important ingredients. The Occidentals are just as proud of their blatantly excessive food intake as the Orientals are of their semistarvation diets."

—I. Snapper. *Annals of the New York Academy of Sciences* 63: 92, 1955.

Abstracts of Current Literature

ABSTRACTERS

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OBESITY: CURRENT THEORIES AND OBSERVATIONS

The problem of obesity has been attacked with fresh vigor in recent years. A considerable literature has accumulated on the mechanisms of lipogenesis and of fatty acid oxidation at the enzyme level involving the 2-carbon fragments and coenzyme A, as elucidated by Lipmann. Obesity appears to have several etiologic bases, among which are genetic, psychological, and environmental elements. The intimate relationship between caloric intake and the expenditure of energy governs the rate at which fat is accumulated or disposed of. Habitual overeating and reduced physical activity are frequently the basic difficulties which lead to obesity.

Obesity—A Brief Review of the Problem. G. H. Berryman. *Metabolism* 3: 544, 1954.

The author discusses the importance of obesity as a hazard to health and longevity, recounting the numerous disorders associated with or aggravated by it. The differentiation between obesity and an increase in the lean body mass as the cause of excessive weight is emphasized. The metabolic pathways involving fat utilization and lipogenesis are presented in relation to fat storage. The customary references to compulsive psychoneurotic overeating are quoted, showing that obesity is frequently related to the desire for affection, the overcoming of depression, etc. The regimens effective in weight reduction are the establishment of a caloric deficit, high protein, moderate fat and carbohydrate diets, and relatively frequent small feedings. An increase in energy output through moderate exercise is recommended. A basic diet plan for achieving weight re-

duction is presented which provides general nutritional adequacy. Proper motivations for weight reduction must be provided in order to succeed in the pursuit of leanness. The caloric levels of reducing diets should be considerably higher than that of the diets usually recommended if long-term weight reduction is to be attained.—C. R. SHUMAN

Much emphasis is placed upon anxiety and insecurity as the basic forces in overeating and obesity. This is undoubtedly true in selected instances; however, not everyone is prepared to accept this concept as explaining the existence of obesity in many of these patients.

What Can Be Done for the Obese Patient? C. M. Young, N. S. Moore, K. K. Berresford, and B. M. Einset. *Am. Practitioner & Dig. Treat.* 6: 685, 1955.

Experience in a community nutrition clinic with 168 obese patients referred by private physicians revealed successful therapy in only about one-fourth of the group. Some success was obtained in another fourth.

Weight reduction was particularly difficult in those who had been obese since childhood. The apparent emotional stability of the subject seemed to be a significant determining factor. Those who appeared emotionally stable were most successful in reducing. The more tense, anxious, and insecure subjects had less success in weight reduction.

A great need exists for some means of evaluating emotional stability of patients before therapy is instituted, in order to determine suitability for treatment. The authors feel that the only real answer to the obesity problem is prevention. Therapy should be limited to the emotionally stable, and given preferably at an early stage.—S. O. WAIFE

Reflections on So-called Endogenous Obesity. G. Dreyfus. *Presse méd.* 61: 321, 1953.

If overeating plays a major role in the development of obesity, it is nevertheless true that a factor of personal predisposition merits consideration in the case of every obese person. The author points out that there is no such thing as a specifically thyroid, pituitary, or genital obesity. It is with the hypothalamic centers of nutritional regulation that the problem of so-called endogenous obesity is concerned. Every case of obesity results from the association, in varying proportions, of exogenous and endogenous factors.—H. GOUNELLE

Eating at night seems to characterize a fairly large segment of our population; it is a habit perhaps derived from late television viewing, after-theater activities, and other evening engagements. In the subjects reported below, there may be a peculiarity in the metabolic pattern which induces excessive eating during the nocturnal hours and leads to obesity.

The Night-eating Syndrome. A. J. Stunhard, W. J. Grace, and H. G. Wolff. *Am. J. Med.* 19: 78, 1955.

The syndrome under discussion consists of nocturnal hyperphagia, insomnia, and morning anorexia in obese subjects. It is described in 20 of 25 obese patients treated in a special study clinic and in none of 38 non-obese subjects. The etiology is undetermined but may be related to a disturbance in the mechanisms involved in controlling appetite so that the arteriovenous blood glucose difference and hypoglycemia may develop in the evening hours with decreasing satiety; or, evening anxiety may develop which is overcome by ingestion of food. Weight reduction is difficult for these patients. It is apparent that Dextadrine® cannot be used as an anorexigenic agent for them, due to interference with sleep. Severe anxiety reactions were observed in several of these patients when dietary restrictions were enforced. It is suggested that this syndrome is part of a response to stress peculiar to certain obese patients and may be related to the pathogenesis of their obesity.—C. R. SHUMAN

The use of calipers to measure skin thickness in gauging body fat represents a method of great potential value, since body composition measurements are technically difficult. Even the composition of adipose tissue is still under study.

Design and Accuracy of Calipers for Measuring Subcutaneous Tissue Thickness. D. A. W. Edwards, W. H. Hammond, M. J. R. Healy, J. M. Tanner, and R. H. Whitehouse. *Brit. J. Nutrition* 9: 133, 1955.

A considerable proportion of the body fat lies in the subcutaneous tissue, which, in many parts of the body, is only loosely attached to the underlying tissue and can be pulled up between the thumb and forefinger into a fold. The thickness of this fold of skin and subcutaneous tissues can be measured by applying some form of caliper to either side of it, and this technique has been widely used to give an estimate of body fat by those concerned with nutrition, with fat distribution, with child growth, and with anthropometric surveys. However, the observed thickness depends on how the skinfold is picked up and on the design of the caliper with which it is measured. These characteristics have never been properly standardized. For this reason, experiments were carried out to determine the optimal design of skinfold calipers. As a result of these experiments, recommendations were formulated for a caliper to give maximum consistency between duplicate readings. These were: that the face area of skinfold caliper not vary by more than 2.0 g/mm; that the pressure exerted over the range of opening 2–40 mm should not vary by more than 2.0 g/mm; that the pressure should be between the limits of 9–15 g/mm with a recommended standard value of 10 g/mm; that the scale of the instrument should be read at least to 0.5 mm and preferably to 0.1 mm.

A new type of caliper was introduced which meets these requirements and which, in the experience of the authors, is the most satisfactory caliper yet devised. With the new calipers, the standard deviations of the differences between duplicate measurements taken by a single observer at the triceps, subscapular and suprailiac sites were 2–4 units in the logarithmic scale, equivalent to 0.3–0.6 mm at a jaw opening of 7 mm. The equivalent figures for different observers were roughly twice these values when the sites for measurement were marked on the body. Observers tended to give slight but consistent differences in readings on any one subject, and these differences varied to a small extent from one subject to another. The choice of sites to be measured for specific problems has not been considered in this study.—B. SURE

The Caloric Value of Labile Body Tissue in Obese Subjects. V. P. Dole, I. L. Schwartz, N. A. Thorn, and L. Silver. *J. Clin. Investigation* 34: 590, 1955.

After a suitable control period, 5 obese healthy women were placed on a constant composition diet, with caloric excess and deficit in alternation. By statistical analysis the changes in weight could be correlated with dietary variations; they could also be separated from the general weight trend and from random changes in water balance.

The "caloric equivalent" is the ratio of the change in caloric intake to the change in weight. These analyses revealed a caloric value of only about 2.5

cal/g—evidence that a considerable amount of water is stored and released as part of the weight response to caloric alterations.

The daily requirement for maintenance on the special diet (previously published, *Am. J. Clin. Nutrition.* 2: 336, 1954) was 20.2 to 24.4 cal/kg/day.—S. O. WAIFE

Obesity in children is interwoven with height and growth and, as the following study indicates, it is a matter of considerable importance.

Obesity in Childhood. A Study of the Birth Weight, the Height, and the Onset of Puberty. O. H. Wolff. *Quart. J. Med.* 24 (N. S.): 109, 1955.

Claims that obese children were already overweight at birth are not supported by this careful study of 100 children seen at the Obesity Clinic of the Children's Hospital in Birmingham. Neither was any evidence found of delayed puberty and genital underdevelopment in obese boys.

On the contrary, the difference between the mean birth weight of obese and normal children was insignificant. Even if the mean birth weight of the most obese group was calculated separately, no significant difference emerged. These findings would certainly suggest that most childhood obesity is acquired and can be prevented by controlling the caloric intake.

In comparing the rate of development of obese children with that of English children as a whole, it was found that the height of obese children averaged 1.6 inches above the standard; however, this highly significant difference did not obtain when their height was compared to the average for English children of the professional classes.

Onset of puberty was found to be earlier in obese children, male as well as female. In obese girls, puberty occurred about a year earlier than in girls of average height (13.6 years) and 6 months earlier than in girls above median height (13 years). Thus, half of the obese girls between 12 and 13 years of age had begun to menstruate. Pubertal development in obese boys was similarly early—about a year earlier than in normal boys of average height, and 6 months earlier than in boys above average height.

In 82 of the children (33 boys and 49 girls), height gain was observed during a weight reduction program. Height gain in children who showed a monthly weight loss of 2 per cent or more of their standard weight was 14.8 per cent less than their expected height gain. Children whose monthly weight loss was less than 2 per cent of their standard weight, who did not lose weight, or who gained weight, showed a height gain 4.6 more than their expected height gain (a statistically significant difference).

In commenting on these very important findings, the author suggests that weight reduction is not contraindicated in obese children and may even be de-

sirable. These children are already taller than average, and the slight retardation of growth occurring during weight loss can do no harm. Indeed, it may do some ultimate good, since growth stops 4 or 5 years after onset of puberty, and obese children may thus turn out to be shorter than average in maturity. Furthermore, if Sinclair and McCance are right in opposing the concepts of "maximum" and "optimum" growth rates, and in correlating early overnourishment with early maturity and early death, then it might be well to prevent the early onset of puberty seen in these children by controlling their caloric intake.—C.-J. HOWELL

The importance of a low caloric intake in the presence of acute cardiac disease is based upon the lowering of body metabolism and reduction of cardiac work associated with dietary restriction. Weight reduction should be enforced when obesity is present for reasons presented below.

Physiologic Effects of Obesity upon the Heart. The Incidence of Obesity in Coronary Disease. A. M. Master and H. L. Jaffe. *J. Am. Geriatric Soc.* 3: 299, 1955.

The relationships between obesity and coronary disease are here summarized in a review of clinical and statistical data.

While obese persons frequently have "cardiac" symptoms—dyspnea, palpitations, etc.—no actual cardiac abnormality can be demonstrated. The cardiovascular symptoms of uncomplicated obesity are probably the result of the increased pulse rate and blood pressure, with concomitant decrease in work tolerance, and they are eliminated by weight reduction. Cardiac output and arteriovenous oxygen difference after exercise are also normal in obesity, but the vital capacity is reduced, and cardiac and respiratory rates, blood lactic acid, and oxygen consumption and debt are increased, with faster, shallower respirations than in persons of normal weight. These findings, plus teleoroentgenogram and electrocardiographic studies, indicate that there is no real abnormality of the heart in obesity, merely a mechanical interference with its function, caused by its elevation and displacement to a transverse position, limitation of respiratory movement, compression of the lungs with consequent reduction of vital capacity, and perhaps the additional burden of supplying the excess fatty tissue through an increased capillary bed. The additional cardiac work demanded by increased surface area and accompanied by increased total body metabolism and oxygen consumption has been successfully reduced by weight reduction, which results in decreased oxygen consumption, increased A-V oxygen difference (indicative of improved oxygen utilization), and a considerable fall in cardiac output and work. Hence the benefits of low calorie diets in anginal syndromes and coronary occlusion; mortality

in patients with acute coronary occlusion has been reported to have been significantly reduced by an 800-calorie diet.

Analysis of the familiar statistics on obesity in coronary disease leaves no doubt that they are somehow correlated. In angina pectoris, in acute coronary insufficiency, and in coronary occlusion, the frequency of overweight and obesity has been found to be about twice as great as among controls. Despite these undoubtedly significant findings, we are not yet certain what they signify. A common metabolic fault may underlie both obesity and coronary disease. Gofman's observation of increased S_r particles in the blood in coronary disease, as well as in obesity, has yet to be adequately explained, and any attempt to establish obesity as the "cause" of coronary disease is still premature.—C.-J. HOWELL

The Action of Chorionic Gonadotrophin in the Obese. A. T. W. Simeons. *Lancet* 2: 946, 1954.

"Simple obesity" has been treated in some 500 cases by daily injections of 125 IU of chorionic gonadotrophin. When patients were allowed to continue their usual diet, the treatment reduced the hip and waist measurements within ten days, but without loss of weight. There was always loss of appetite. When patients were restricted to two meals daily, each consisting of "100 g of lean meat, a normal helping of leafy vegetables, an unsweetened rusk, and an apple or the equivalent in fruit, with salt and fluids *ad lib.*," they lost from 250–600 g daily, "without any inconvenience . . . even doing a hard day's work." After about 40 days' treatment and the loss of 20–30 pounds, normal appetite returned, there apparently being an "immunity" to the action of the hormone; this lasted about 6 weeks, after which another equally effective course could be given. Patients were usually able to maintain the weight reached after treatment, although they became weak and hungry if they continued their 500-calorie diet. When, during a course of treatment, saline injections were substituted for the gonadotrophin, the weight loss continued for about three days, after which the patients complained of weakness, became irresistibly hungry, and either ate secretly or felt unable to continue treatment. No vitamin deficiencies were noted in treated patients, but there was occasional hypoglycemia which could be corrected by a teaspoonful of sugar.

Other conditions often associated with obesity improved: overweight diabetics whose weight was reduced in this way often developed a normal blood sugar which remained normal as long as they did not gain weight again. Gout, and a number of dermatoses improved after treatment, and peptic ulcers, although they did not heal, became symptomless. There was an increase in libido and often in fertility in previously overweight women.

The author concludes that, although chorionic gonadotrophin alone does not reduce weight, it does

make a very drastic calorie curtailment possible.—F. E. HYTTEN

The following abstracts, from the active Harvard group, deal with the theory that food intake is governed by appetite as well as other physiological, psychological, and genetic factors. In addition, the utilization of fat appears to be regulated differently in several experimental types of obesity under study. Food intake may be controlled by "glucoreceptors" present in the hypothalamus which are sensitive to arteriovenous differences in the glucose levels. Hunger is experienced when the arteriovenous blood glucose differences approach zero. In genetically obese, hypothalamically obese, and goldthiogluucose obese animals, certain metabolic patterns are emerging which characterize these conditions, as described in this series of six abstracts.

Fat Metabolism in Three Forms of Experimental Obesity. Body Composition. M. W. Bates, S. F. Nauss, N. C. Hagman, and J. Mayer. *Am. J. Physiol.* 180: 301, 1955.

Three forms of experimental obesity were studied: (1) hereditary obese-hyperglycemic mice; (2) mice made obese by goldthiogluucose injections; (3) rats made obese by hypothalamic injury. Increased fat accounted for more than 90 per cent of the weight increase in all three forms. In obese and nonobese animals the fat is chemically similar. The protein content of the body was markedly lower in young obese-hyperglycemic mice. Both young and mature animals of this same group were found to have a greater body cholesterol content.—M. J. OPPENHEIMER

Fat Metabolism in Three Forms of Experimental Obesity. IV. "Instantaneous" Rates of Lipogenesis in Vivo. M. W. Bates, C. Zomzely, and J. Mayer. *Am. J. Physiol.* 181: 187, 1955.

C^{14} -carboxyl-labeled acetate was injected into the peritoneum and its retention in carcass and liver lipids was studied after 30 minutes in experimentally obese animals. Adipose tissue was the site of most of the synthesis. Fasting has a more marked influence on liver lipogenesis than on that of peripheral tissues, while diet has a greater effect on liver. Under a regimen of *ad libitum* feeding, obese animals synthesized more liver and carcass fat than the control group. However, during fasting, obese-hyperglycemic mice produced more fat than normal, although goldthiogluucose obese mice and hypothalamic rats did not do so.—M. J. OPPENHEIMER

Fat Metabolism in Three Forms of Obesity. V. Hepatic Lipogenesis in Vitro. J. Mayer, N. C. Hagman, N. B. Marshall, and A. J. Stoops. *Am. J. Physiol.* 181: 501, 1955.

The test animals used were obese on a genetic basis, or as a result of goldthioglucose or because of hypothalamic lesions. Liver slices from these and control animals were incubated with C^{14} -carboxyl-labeled acetate. The authors then determined the amount of C^{14} which was incorporated into fat. If the animals were fed there was an increase in lipogenesis in all three types above that observed in controls. This was true whether the results were expressed on the basis of each liver or per gram of fat-free tissue. However, in fasted animals fat synthesis was less than that of controls. Nevertheless, there was a difference in the three types. The depression in genetically obese mice was markedly less than that observed in goldthioglucose and hypothalamic obese subjects. Two different types of obesity seem to be represented. Since in goldthioglucose and hypothalamic obesity increased hepatic fat synthesis after feeding is depressed by a subsequent fast, this indicates that factors which preside over food intake are at fault in permitting increased lipogenesis. A basic error in metabolism is indicated in genetic obesity, since increased hepatic lipogenesis persists although a fast is imposed.—M. J. OPPENHEIMER

Fat Metabolism in Three Forms of Experimental Obesity. Fatty Acid Turnover. M. W. Bates, J. Mayer, and S. F. Nauss. *Am. J. Physiol.* 180: 309, 1955.

C^{14} -carboxyl-labeled palmitic acid was used in these studies. The animals were fed this material and the decline in isotope content of carcass fat was measured against time. The fat turnover was 50-60 per cent of control values in mice. Hypothalamic rats turned over less than 5 per cent of the amount which was observed to be turned over by normal controls. These results indicate different metabolic patterns for the various kinds of obesity.—M. J. OPPENHEIMER

Fat Metabolism in Three Forms of Experimental Obesity. Acetate Incorporation. M. W. Bates, J. Mayer, and S. F. Nauss. *Am. J. Physiol.* 180: 304, 1955.

In these studies, C^{14} -carboxyl-labeled acetate was used. This material was fed to obese mice and rats. Obese-hyperglycemic mice and hypothalamic rats retain more C^{14} in carcass lipids than controls when they are losing weight. This is not true of goldthioglucose obese mice, which retain the same amount as control animals. If weights are maintained, all types of obese mice and rats retain more C^{14} than do controls. Carcass fat content, strains, and state of nutrition were adequately controlled. Differences in uptake, therefore, depend on different metabolic patterns in the different kinds of obesity.—M. J. OPPENHEIMER

Energy Balance in Goldthioglucose Obesity. N. B. Marshall and J. Mayer. *Am. J. Physiol.* 178: 271, 1954.

Goldthioglucose induced obesity in LD₅₀ doses when dissolved in water. Goldthiomalate and sodium thioglucose were ineffective. In the obese mice food intake was increased 75-100 per cent; oxygen use was elevated, although physical activity was similar to nonobese controls. Genetically obese mice have a slight hyperphagia, low oxygen uptake, and decreased physical activity. Goldthioglucose mice gain weight most rapidly on high fat diets, gain less on high protein diets. This is similar to hypothalamic hyperphagic mice but different from genetically obese mice.—M. J. OPPENHEIMER

The contrast between the results reported in this work and those reviewed above indicates that further studies are required.

Studies in Acetate Metabolism in the Hereditary Obesity—Diabetes Syndrome in Mice Utilizing C^{14} Acetate. W. Parson and K. R. Crispell. *Metabolism* 4: 227, 1955.

Obese mice studied by Mayer did not catabolize acetate at the same rate as nonobese animals, leading to the conclusion that a block in acetate utilization was a factor producing increased lipogenesis as the biochemical lesion responsible for the syndrome. In repeating these experiments, the present authors administered carboxyl-labeled sodium acetate to obese and nonobese mice. The elimination of $C^{14}O_2$ was measured. The results showed that obese mice eliminated more CO_2 ; the total radioactive CO_2 elimination revealed that obese mice catabolized the injected acetate as well as the nonobese mice. The reasons for the discrepancy between this work and that previously reported by Mayer are not apparent.—C. R. SHUMAN

DIGESTION AND ABSORPTION OF FATS

Dietary fat is hydrolyzed by lipases derived from the pancreatic juice and succus entericus. The products of hydrolysis are the fatty acids and glycerol, both of which are absorbed by the mucosa. Some of the fatty acids are esterified with cholesterol; others are reconstituted into fat within the mucosa, combining with dihydroxyacetone. These findings tend to support the hydrolytic theory of fat digestion. The transport of fat as chylomicrons and as phospholipids and cholesterol esters in the form of lipoproteins is recognized.

Digestion of Neutral Fats by Human Subjects. R. S. Harris, J. W. Chamberlain, and J. H. Benedict. *J. Clin. Investigation* 34: 685, 1955.

There are two theories to explain the digestion of fat: the *hydrolytic*, in which fats (triglycerides) are broken down completely to fatty acids and glycerol, which are then absorbed, and the *particulate* theory, in which fat is partially hydrolyzed in the intestine

to monoglycerides, diglycerides, and fatty acids. The result is an emulsion of partial glycerides, triglycerides, fatty acids, and bile salts which enter the intestinal walls.

In this careful and detailed study, healthy young male subjects drank melted vegetable fat (soybean and cottonseed oil) and by intubation the partially digested lipids were recovered and analyzed. It was found that appreciable quantities of monoglycerides and free fatty acids were present at almost all periods of digestion. Fat digestion in a more conventional meal was also studied in these subjects, who ate toast, margarine, jelly, sugar, and coffee. There was no significant difference in the proportion of fat digestion products when fat was incorporated into a meal and when it was fed alone.—S. O. WAIFE

Mechanism of Intestinal Absorption of Fat. A. C. Frazer. *Nature* 175: 491, 1955.

The changing ideas about intestinal fat absorption, from Pflüger's lipolytic hypothesis until the present day, are briefly annotated. The replacement of the lipolytic theory by the modern one of partition has involved three main conceptual changes. They are:

"(1) Complete hydrolysis of glycerides to fatty acids and glycerol is not an obligatory step in the process of fat absorption.

"(2) Lipids do not have to be brought into water-soluble form before they can be removed from the small intestinal lumen.

"(3) Eventual partition of the lipid molecules between the oil and the water phase may affect their distribution in the body after absorption."—F. E. HYTTEN

A Study on the Intestinal Absorption of Fat in Normal Adults and in Non-tropical Sprue with Carbon-labelled Oleic Acid and Palmitic Acid. R. Blomstrand. *Acta Med. Scandinav.* 152: 129, 1955.

Fatty acids were labeled with carbon¹⁴, incorporated into olive oil, and fed to two normal subjects. It was found that 99.4 per cent of the labeled fatty acids were absorbed. The results also supported the concept that in normal adults the amount and character of fecal lipids are not greatly influenced by alterations in food fats.

In a patient with non-tropical sprue, 76.5 per cent of the administered labeled fatty acids were absorbed. Analysis revealed that unabsorbed dietary fatty acids constituted the major part of the fecal fatty acid. A certain portion, however, was non-dietary in origin and represented bacterial material or mucosal desquamation.—S. O. WAIFE

Note the conflicting results reported in the following abstracts concerning the effect of sitosterol upon the lipid fractions of human serum. Such differences have appeared in numerous other investigations thus far reported with the use of this substance.

The Effects of Sitosterol on Serum Lipids. M. M. Best, C. H. Duncan, E. J. Van Loon, and J. D. Wathen. *Am. J. Med.* 19: 61, 1955.

The influence of the plant sterol, beta-sitosterol, on serum cholesterol, other lipids, and on lipoproteins was studied using 20 to 25 g of the substance given daily for prolonged periods to 14 patients on free diets. A sustained lowering of serum total cholesterol with a concomitant reduction in total lipid, neutral fat, and lipid phosphorus was observed. Less evident was a trend toward lower lipoprotein levels of S₁ 3-10, 10-30, and 30-100 classes. The effects of sitosterol are attributable to interference with dietary and endogenously-formed cholesterol. The reduction in serum neutral fat may be secondary to a lowering of cholesterol absorption, although this feature requires further study. Sitosterol apparently competes for esterification in the process of cholesterol absorption. This substance has been found non-toxic and is worthy of further study since it produces desirable effects in atherosclerotic states.—C. R. SHUMAN

The Effect of Varying the Intake of Dietary Fat and the Ingestion of Sitosterol on Lipid and Lipoprotein Fractions of Human Serum. C. F. Wilkinson, Jr., E. Boyle, R. S. Jackson, and M. R. Benjamin. *Metabolism* 4: 302, 1955.

The effect of decreasing the fat content of the diet and that of sitosterol administration upon serum lipoprotein determined by ultracentrifugation and upon serum lipid fractions were determined in a group of seven patients with lipid disturbances. The "total stool cholesterol" was also measured. Diets providing less than 0.25 g of fat per day produced a variable degree of depression of total serum cholesterol. In 5 of the 7 patients, the downward trend of cholesterol was arrested or reversed during the second week of fat restriction. The low fat regimen appeared to decrease the phospholipid/cholesterol ratios of the normo-cholesterolemic subjects. Sitosterol was added to diets of choice or to diets containing 49 g of vegetable fat daily. Nevertheless, serum cholesterol was not altered over periods up to 35 weeks with this addition. The administration of vegetable fat and sitosterol was associated with a return of all lipoprotein values to or above control levels. The excretion of digitoxin-precipitable, Liebermann-Burchard-positive material in the stool appeared to be independent of fat intake and could not be correlated with serum cholesterol changes.—C. R. SHUMAN

An interesting observation on the lower cholesterol levels of rural persons consuming high caloric intakes has been explained on the basis of an increased rate of energy turnover in these subjects. This concept is supported by the low body weight of these subjects despite a caloric intake exceeding the Recommended Allowances. Further studies of this type under some-

what more controlled conditions are awaited for confirmation of this work.

The Serum Lipoprotein and Cholesterol Concentrations of Central and North Americans with Different Dietary Habits. G. V. Mann, J. A. Muñoz, and N. S. Scrimshaw. *Am. J. Med.* 19: 25, 1955.

Total cholesterol and beta-lipoprotein measurements were made on a group of rural Central American subjects subsisting on a low fat, largely vegetarian diet, for comparison with similar studies on urban Guatemalans and North Americans eating large amounts of fat. At all age levels the rural Central American subjects showed lower mean cholesterol levels than the other groups and no sex difference was observed at any age level. The cholesterol levels did not tend to rise with age as has been observed in North American subjects. The cholesterol levels of urban Guatemalans were similar to those of North Americans. The beta-lipoproteins of the female Central Americans were frequently higher than those of North Americans, while the males exhibited slightly lower levels. The differences, however, among the groups were variable; urban Guatemalans showed levels as high or higher than those of North Americans. The rural Central Americans have a caloric intake which is 10 per cent in excess of the National Research Council's allowance, and yet they were, on an average, 15 per cent leaner than the other groups. These findings suggest that the serum lipoprotein levels may be dependent on the energy turnover, whereas cholesterol levels, which were low in the rural group, are increased by energy accretion or fat deposition. The differences in fat intake fail to explain serum lipid differences in these groups since they do not explain the dissociation between cholesterol and lipoprotein levels in rural Central Americans.—C. R. SHUMAN

In the human, obesity is associated with a shortened life span, as indicated by mortality statistics. However, there is little information concerning the effect of a high fat diet in the absence of obesity upon the life span of the human. In experimental animals, the feeding of a high fat diet appears to be injurious.

Life Span of Mice Fed a High Fat Diet at Various Ages. R. Silberberg and M. Silberberg. *Canad. J. Biochem. & Physiol.* 33: 167, 1955.

A large number (441) of male mice of a closely inbred strain were used in feeding experiments: some were on a 30 per cent fat diet from one month of age, others for a limited time, some beginning in early life, and some after one month, 6 months, and 12 months.

When the mortality of the groups was compared to the control (on a 5 per cent fat stock diet), it was found that (a) feeding of a high fat diet from ages

1, 6, or 12 months on shortened the life span; (b) if the high fat diet was given for a limited period of time, the longevity effect depended on the age at which the mice were placed on the ration.

Given during the growth period, the high fat ration did not alter the life span. On the other hand, a fat-enriched ration in older animals seemed injurious. In short, age differences exist in regard to susceptibility to dietary imbalances.—S. O. WAIFE

Influence of Previous Diet on Hepatic Glycogenesis and Lipogenesis. J. E. Whitney and S. Roberts. *Am. J. Physiol.* 181: 446, 1955.

High fat diets were fed for two to three months. As a result of this regime the *in vitro* incorporation of isotopic methyl carbon of acetate into liver glycogen and fatty acids was depressed in fed animals. On the other hand, in fasted rats which had previously been on a high fat diet, there was a stimulation of the incorporation of isotope into hepatic cholesterol. The data presented suggest that the observations may be explained on the basis of depressed glycogenesis and fatty acid synthesis. At the same time, cholesterogenesis is increased in the livers of the animals which have been fat-adapted. It is possible that prolonged fat feeding establishes these adaptations and that they persist in the early period when a fast is imposed.—M. J. OPPENHEIMER

The value of neutral fat emulsions in the intravenous alimentation of human patients has been demonstrated in several studies reported from various centers in this country. With further perfection of these preparations to eliminate the occasional untoward reactions observed, the problem of supplying adequate calories in the postoperative patient will be overcome.

Clinical Experience with Intravenous Infusion of Emulsified Fat. W. R. Waddel, R. P. Geyer, F. R. Olsen, S. B. Andrus, and F. J. Stare. *J. Lab. & Clin. Med.* 45: 697, 1955.

This article by the group from Harvard who have had extensive experience with parenteral fat preparations is a compilation of their accumulated clinical experience with various fat emulsions. They review their results with 1466 infusions into 426 patients, most of whom were seriously ill with either intra-abdominal malignancy or infection. The bulk of the paper deals with the nature of the reactions observed and their relations to various fats used in the emulsion, as well as to other possible variables. No information is given on the utilization or metabolism of the fat, this information having been published elsewhere.

The most common reaction was a thermogenic one. A rise above 2° F. was considered intolerable and the infusion generally stopped. Using this criteria, 97 per cent of the cottonseed oil infusions (the one

in general use at the present time) were tolerable, as were 94 per cent of all infusions of synthetic triolein. Ninety-one per cent of cottonseed oil emulsions, 86 per cent of coconut oil, 82 per cent of olive oil, 85 per cent of coconut oil-olive oil, 83 per cent of peanut oil, and 76 per cent of triolein were without any pyrogen reaction.

Other side-effects noted were chills; severe to moderate pain, usually in the back but also seen in the chest, legs, and arms, which comes on in a few minutes after the infusion is started and disappears after a short interruption; vasomotor changes, primarily a rise in systolic blood pressure and pulse, which subside upon slowing the infusion; various allergic phenomena; nausea, vomiting, anorexia, and headache. None of the aforementioned side-effects seemed to be correlated very well with either the concentration or the nature of the oil. There did seem to be a relation between the vasopressor effect and the phosphatide used as the emulsifier. There was no relation between the level of the serum proteins and reaction rate, nor could these various reactions be affected by the administration of 25 mg of Pyribenzamine added directly to the 600-ml bottle of fat emulsion.

The reported incidence of adverse reactions, particularly the febrile ones, is quite low compared to those observed by others where the incidence ranges up to 50 per cent. This may well represent a superior emulsion. However, as far as the fever response is concerned, it should be noted that temperatures were recorded at 20-minute intervals the first hour, hourly during the infusion, and then obtained from the regular hospital chart which presumably would be at four-hour intervals. This procedure could well miss significant temperature rises. Not mentioned by this group, but known to the abstractor to have happened, is the rare occurrence of an anaphylactoid-like reaction following the administration of a few ml of a fat emulsion. There have been no reported instances of fatality, however.

Until more is known about some of the physicochemical properties of fat and the chylomicron, and better methods provided for the preparation of fat emulsions, there are bound to be variations in batches of prepared material which will lead to variable reactions. The problem is by no means solved, but work like that reported here is going on at several centers throughout the country and certainly the goal will be achieved in the near future.—J. F. MUELLER

The use of low fat diets in the treatment of multiple sclerosis has been reported in several articles by Dr. Swank, one of which is summarized below. Further observations upon the relationship of dietary fat to this disease are anxiously awaited.

Treatment of Multiple Sclerosis with Low-Fat Diet. R. L. Swank. *Arch. Neurol. & Psychiat.* 73: 631, 1955.

Five and one-half years' experience with a low fat diet in the treatment of multiple sclerosis is summarized. This diet appears to lessen the severity of the disease by reducing the frequency and severity of the exacerbations. Its usefulness is greatest early in the disease, before significant disability and a steady progression of symptoms have developed.

The mechanism by which the fat intake might influence the disease is discussed. It is hypothesized that the neurological lesion in multiple sclerosis may be due to tissue ischemia resulting from a breakdown of the suspension stability of the blood. It is suggested that this altered state of the blood is precipitated by large fat meals in persons presumed to possess an inherent metabolic defect. The appendix includes a recommended low fat, high carbohydrate, moderate protein diet.—S. W. CONRAD

VITAMIN B₁₂

The effectiveness of vitamin B₁₂ supplementation of diets of undernourished children has not been adequately confirmed, although a growing number of reports have appeared indicating a beneficial weight gain, increased height, and improved appetite following the use of the vitamin in growth failure. Additional studies, including those showing negative results, are needed for a complete evaluation. In several controlled experiments with a constant caloric intake, vitamin B₁₂ has not been effective, suggesting that improvement of appetite and increased consumption of food is an important factor in the favorable action of vitamin B₁₂ reported elsewhere.

The Use of Partial Vitamin Supplements in the Treatment of Growth Failure in Children. J. Crump and R. Tully. *J. Pediatrics* 46: 671, 1955.

A mixture of 25 µg of vitamin B₁₂ and 10 mg of vitamin B₁ was administered daily to 50 undernourished children whose ages ranged from 3 to 12 years. These children were selected from private practice and had been observed for at least one year prior to the administration of the vitamins. The majority of the subjects had a poor appetite and/or retardation of growth and development. Two overweight children who showed no response and 12 patients who received the vehicle without vitamins were included in the study. The vitamin supplement was continued for at least one year and in some cases beyond two years.

The parents reported that a definite beneficial response followed the use of these vitamins. Data on height and weight were adequate in 32 cases to permit analysis by the Wetzel Grid technique and revealed positive channel and auxadrome shifts in 88 per cent of 18 children with simple growth failure. There was no response in those cases which failed to demonstrate growth failure. Chronically ill children do not differ substantially from those with no evidence of disease.

The improvement in appetite was uniformly observed in the group receiving vitamin B₁₂ and B₁ but not in the 12 children who received the vehicle alone. No mention is made of the height and weight in the latter group during comparable periods of observation.

This report confirms the observation of Wetzel, Chow, and more recently of Larcomb. These benefits are to be attributed to stimulation of the appetite by these agents rather than to a specific influence on growth and development.—J. N. ETTELDORF

Effects of Vitamin B₁₂ and Aureomycin on Nitrogen Retention in Infants. R. Kaye, H. Caughey, and W. W. McCrory. *Pediatrics* 13: 462, 1954.

Individual nitrogen and electrolyte balance studies were conducted on malnourished children in order to obtain information concerning the anabolism of protein following the administration of vitamin B₁₂ and aureomycin. The subjects studied were male infants ranging between 3 and 12 months whose weights varied from 3.8 to 7.4 kg. The caloric intake remained fixed and thereby eliminated the appetite-stimulating effect of vitamin B₁₂. Three infants were placed on a high protein diet (1 g/kg/24 hr) and 3 on a low protein diet (0.1 g/kg/24 hr). The influence of aureomycin was studied on two infants receiving the low protein intake.

There was no significant increase in weight as a result of vitamin B₁₂ in either group; as would be anticipated, the high protein diet resulted in a considerably greater gain in weight (11.8, compared to 2.4 g/kg/24 hr in the group receiving the low protein diet). The administration of aureomycin in conjunction with vitamin B₁₂ caused an insignificantly greater increase in weight (0.3 g/day), when compared to a period when vitamin B₁₂ alone was administered to two infants while on a low intake of protein.

Vitamin B₁₂ resulted in a decrease of 26 per cent in nitrogen retention in the subjects with a high protein intake and was considered to be of "doubtful significance" because it represented only 8 per cent of the total intake. In two infants on a low protein intake, there was an increase of 17 per cent in the nitrogen retention during the period of vitamin B₁₂ administration. This was considered to be insignificant in such a small series, with 80 per cent of the increase being contributed by one individual. Aureomycin exerted no influence on the nitrogen retention and increased fecal nitrogen loss.

Urinary nitrogen excretion was increased by vitamin B₁₂ in the group receiving a high protein intake. This observation, when correlated with no change in absorption and a decrease in retention of nitrogen, was interpreted to indicate a probable increase in the rate of conversion of protein to carbohydrate and fat. The excretion of urinary nitrogen was decreased from 77.5 to 66 per cent when vitamin B₁₂ was administered to the group receiving the low protein intake; how-

ever, the fecal nitrogen was not influenced and therefore the absorption of nitrogen was not significantly altered by the vitamin. Nitrogen equilibrium was established on a diet of 0.1 g of cow's milk protein which corresponds to 20 per cent of the usual intake.

All infants remained in positive Na, K, and Cl balance during the experimental and control periods.

These results confirm the clinical observation that the benefits derived from vitamin B₁₂ are mediated chiefly through its ability to stimulate appetite. The more recent claims of beneficial effects from a combination of tetracycline derivatives and vitamin B₁₂ also appear unjustified. For the sake of completeness, it would have been interesting if the authors had accumulated data on the effect of this combination in malnourished children while on a high protein intake.—J. N. ETTELDORF

Vitamin B-12 and the Growth of Children: A Review. J. A. Campbell and J. M. McLaughlan. *Canad. M. A. J.* 72: 259, 1955.

The total literature dealing with growth-promoting effects of vitamin B₁₂ is reviewed. On the basis of this review, it is apparent that no conclusions can be drawn pro or con at the present time. The only really controlled study, which appears to show a growth-promoting effect of vitamin B₁₂ in underweight children on low protein diets, is that of Jolliffe *et al.*, published in the *Nutritional Symposium Series* No. 7, National Vitamin Foundation, July, 1953. Additional work is needed.—L. W. KINSELL

Investigation of the blood levels of vitamin B₁₂ has shown a reduction in several groups of subjects: (a) in vegetarians and malnourished groups; (b) in some pregnant and lactating females; (c) in those with absorption defects, as in pernicious anemia; and (d) in some older individuals.

Some Observations on the Metabolism of Vitamin B₁₂ by Jamaican Children. S. J. Patrick. *J. Nutrition* 55: 129, 1955.

The following work was undertaken as part of an investigation of the nutritional status of children in Jamaica, B. W. I.

A group of 19 Jamaican children who had received dietary vitamin B₁₂ supplementation over a period of 9 months had significantly higher plasma B₁₂ concentrations than did a control group. The control group of children had plasma vitamin B₁₂ concentrations which were very similar to those reported for normal American adults by Rosenthal and Sarett (*J. Biol. Chem.* 199: 433, 1952). An attempt to saturate two children by repeated intravenous injections of vitamin B₁₂ resulted in higher "resting" plasma levels of the vitamin. The percentage of the vitamin which was excreted after each test dose did not, however, rise significantly.

Plasma levels and urinary excretion of vitamin B₁₂ after a test dose of the vitamin were compared in (a)

children of retarded growth, (b) the same children after dietary vitamin B₁₂ supplementation, and (c) children with normal growth. No marked differences were observed between the groups in the urinary excretion of vitamin B₁₂ or in the rate of removal of B₁₂ from the plasma. The "resting" level of vitamin B₁₂ in the plasma was, however, raised by the supplementation.—B. SURE

Information on the true vitamin B₁₂ content of foods is urgently needed. Most of the values found in the literature may lack the accuracy of more recent work based on newer information regarding assay methods and the biological activities of vitamin B₁₂ and pseudo-B₁₂.

Vitamin B₁₂ Content of Organ Meats. H. E. Scheid and B. S. Schweigert. *J. Nutrition* 53: 419, 1954.

The microbiological method of assay for vitamin B₁₂ using *L. leichmannii* 327 as the test organism has been further investigated. Additions of KCN, NaNO₂ or thioglycolic acid to the same or assay medium did not improve the assay method over that of short-term autoclaving and subsequent assay with the use of an amino acid medium containing thioglycolic acid.

The vitamin B₁₂ potency of composite samples of liver, kidney, pancreas, spleen, heart, and lung, from beef, pork, and lamb, and of brain and liver from old cows and sows was determined. Liver and kidney were found to be the richest source of the vitamin, and the meats of beef organs were higher in vitamin B₁₂ potency than those of pork. Pancreas was found to contain considerable vitamin B₁₂ activity after alkali treatment when assayed with *L. leichmannii*, but not when assayed with *E. gracilis*. Limitations in the use of alkali lability as an index of the true vitamin B₁₂ potency of samples are discussed.—B. SURE

The author of the following paper is one of the group (Latner, Merrills, and Raine, Lancet 1: 497 and 1134, 1954) responsible for the isolation of what appears to be pure intrinsic factor. The product was obtained from hog gastric mucosa and is a mucoprotein with a molecular weight of about 15,000.

The Binding of Vitamin B₁₂ by Castle's Intrinsic Factor. L. Raine. *Nature* 175: 777, 1955.

The binding capacity of Castle's intrinsic factor for vitamin B₁₂ varies, *in vitro*, with the concentrations of the two substances—the specific binding capacity rising with the amount of excess of the vitamin. It is concluded that these results may throw some light on the clinical observation "which demonstrates that an increase in either the amount of vitamin B₁₂ or of intrinsic factor enhance the haematopoietic effect of their simultaneous oral administration."—F. E. HYTIEN

Satisfactory clinical and hematological responses in pernicious anemia have been repeatedly reported with oral vitamin B₁₂ without intrinsic factor, provided massive doses are employed. However, commercial preparations containing small amounts of vitamin B₁₂ with as little as 0.05 to 0.30 mg of intrinsic factor have proved very effective on an oral daily schedule.

Oral Vitamin B₁₂ in the Treatment of Macrocytic Anemias. W. G. Unglaub and G. A. Goldsmith. *South. M. J.* 48: 261, 1955.

Eleven patients with pernicious anemia and three with "nutritional" macrocytic anemia were treated with large oral doses of vitamin B₁₂ without intrinsic factor material.

It was found that in most cases a satisfactory initial therapeutic response could be obtained by the oral administration of 3000 µg (3 mg) of vitamin B₁₂, and remissions could be maintained on doses of 3000 µg every 4 weeks or 1000 µg (1 mg) a week. However, there was a wide and unpredictable variation in response among different patients.

Oral vitamin B₁₂ therapy appears to be as effective in the treatment of the neurologic complications as parenteral therapy. Serum vitamin B₁₂ levels were subnormal before therapy and during withdrawal relapse in patients with macrocytic anemia.

Two of the three patients with "nutritional" anemia suffered a relapse when specific therapy was withdrawn, although they were eating a nutritionally adequate diet throughout the study. The authors feel that some doubt may be raised as to the "nutritional" origin of at least some of the megaloblastic anemias which are accompanied by free gastric hydrochloric acid.—S. O. WAIFE

The decreased absorption of vitamin B₁₂ following a large parenteral injection may be due to blockade of the "intramural intestinal vitamin B₁₂ acceptor" proposed by Glass (Science 120: 74, 1954).

The Urinary Excretion of Labelled Vitamin B₁₂. S. T. Callender and J. R. Evans. *Clin. Sc.* 14: 295, 1955.

When a large dose of unlabeled vitamin B₁₂ is injected shortly after a tracer dose of ⁵⁷Co-labeled vitamin B₁₂ has been given by mouth, some of the radioactivity appears in the urine.

In both control subjects and in a variety of pathological conditions the results obtained from this urine test correlate well with values derived from the measurement of unabsorbed radioactivity in the feces.

The test described is a simple and rapid method of estimating the absorption of vitamin B₁₂ and the activity of intrinsic factor, and it has the additional advantage of ridding the body of a proportion of radioactive material. There is a suggestion, however, that the absorption of the labeled vitamin from the

intestine may sometimes be impaired by the large parenteral injection.—F. E. HYTEN

The scope of diseases treated with vitamin B₁₂ is very broad. Relatively few of the beneficial reports in diseases other than pernicious anemia appear to be well founded. In the following study, vitamin B₁₂ was tried in schizophrenia.

Massive Doses of Vitamin B₁₂ in Treatment of Schizophrenia. A. D. Pokorny. *Arch. Neurol. & Psychiat.* 73: 345, 1955.

Since vitamin B₁₂ had been used successfully in the treatment of various disorders of the nervous system, such as painful neuropathies, it was decided to try massive doses of vitamin B₁₂ in the treatment of schizophrenic patients. Ten patients were given 1000 µg of vitamin B₁₂ intramuscularly daily in three divided doses, for a period of 30 days, and another ten patients received a similar volume of injection of a placebo.

Six patients of the 20 improved during the month of injections and in the succeeding few weeks. Three of these were in the vitamin B₁₂ group, and three were in the placebo group. Follow-up for periods ranging from 10 to 22 months did not reveal any difference in the two groups in terms of improvement. It was concluded that massive doses of vitamin B₁₂ did not alter the course of schizophrenia.—S. W. CONRAD

Among the several studies involving vitamin B₁₂ the relationship between vitamin B₁₂ and folic acid, as involved in nucleic acid synthesis, is important.

The Relation of Vitamin B₁₂ to Egg Yolk Storage of Folic Acid. B. E. Welch, R. W. Perrett, J. H. Clements, and J. R. Couch. *J. Nutrition* 54: 601, 1954.

The addition of vitamin B₁₂ to a synthetic diet increased the deposition of folic acid and citrovorum factor in egg yolks. The increase in the folic acid content of egg yolk due to vitamin B₁₂ was more apparent when the lower levels of folic acid were fed. The vitamin B₁₂ content of the yolk increased only when the vitamin was added to the diet.

Hatchability was increased by the addition of vitamin B₁₂ to the diet.—B. SURE

NUTRITIONAL AND METABOLIC ASPECTS OF DIABETES

During the pre-insulin era, the management of diabetes involved the use of high fat diets, low in carbohydrate content, introduced by Naunyn and advanced by the studies of Woodyatt, Newburgh, and others. Following the introduction of insulin, the dietary programs for these patients were gradually liberalized until they approximated those of

*normal patients. A practical modification of the diabetic diet was introduced in 1948 by Caso and Stare. The simplicity and adaptability of the new technique of diabetic diet prescription has led to its acceptance in many leading diabetic clinics (Robinson, C. H.: *J. Clin. Nutrition* 1: 309, 1953). The high fat diets previously recommended have been largely discarded because of unpalatability and dangers of increasing lipidemia; however, insulin requirements are lower during periods of high fat intake with carbohydrate restriction.*

Relationship of Dietary Carbohydrate and Fat to Ketonuria in Diabetic and Nondiabetic Subjects. G. T. Perkoff and M. Rosecan. *Metabolism* 4: 214, 1955.

The effects of wide variations in fat and carbohydrate content of isocaloric diets upon the metabolism and excretion of ketone bodies in 3 controlled diabetics, 3 uncontrolled diabetics, and 3 nondiabetic patients were investigated. Infusions of beta-hydroxybutyric acid were administered to 2 patients to examine the utilization of the keto-acids during the feeding periods. Urinary sugar and ketone excretion, blood ketone, and stool fat determinations were performed. The controlled diabetic subjects were found to excrete normal amounts of ketones on a normal diet, with only a minimal rise on the high fat diet. In the unregulated diabetics a marked rise in ketonuria occurred. The high carbohydrate diets sharply reduced ketonuria in all but one diabetic and one of the control subjects. Each diabetic patient required less insulin during the period of high fat intake. A decreased rate of ketone body formation is postulated as the mechanism for decreased ketonuria. The injected ketoacid disappeared at the same rate during both the high fat and high carbohydrate periods. It is suggested that a diet of normal fat and carbohydrate distribution represents the most suitable program for the treatment of diabetic patients.—C. R. SHUMAN

The Food Exchange System employed in this country permits stepwise changes in the diabetic diet. Employing this method, one can increase or decrease the caloric intake as protein, fat, and/or carbohydrate exchanges, depending upon the needs of the individual patient as gauged by weight changes or metabolic status. Apparently a similar method is used in Australia.

Diabetic Diets Simplified: The Core Diet. J. M. Woodhill and J. L. Logan. *M. J. Australia* 1: 960, 1955.

Physicians as well as dietitians will be interested in this attempt at further simplifying diabetic diets. In essence, an 1800- and a 2400-calorie diet are presented. A table of food values permits increases and decreases in 100-calorie steps, e.g., a slice of bread

with butter provides 100 cal and 16 g carbohydrate, etc. With substitutions as presented, it is possible to tailor-make many diets suitable for diabetic persons, varying from a weight reduction program to a high milk diet for a pregnant woman. Many of the recommendations are based on the simplified diet lists prepared by the American Diabetes Association; this article represents a minor but possibly helpful modification.—S. O. WAIFE

The previous elevation of keto-acids described in diabetic patients has been contradicted in the following paper. It may be assumed that the formation of pyruvate is diminished because of the reduction in glucose utilization. A difference in pyruvate response between insulin-sensitive and insulin-resistant diabetics is also noted.

Blood Concentrations of Pyruvic and α -Ketoglutaric Acids in Normal People and Diabetic Patients. (A preliminary communication.) M. J. H. Smith and K. W. Taylor. *Lancet* 1: 27, 1955.

There are conflicting opinions about the blood levels of alpha-keto acids in patients with diabetes mellitus. The authors criticize the older methods of estimation as being non-specific for these acids and describe a new method using 1:2-diamino-4-nitrobenzene to form stable derivatives separable by paper chromatography.

The blood pyruvate, alpha-ketoglutarate, and glucose concentrations were measured in 7 normal and 8 ambulant diabetic subjects receiving insulin; two of the diabetics had a moderate degree of ketosis. There were no significant differences between the two groups in the blood levels of alpha-keto acids. Among the diabetics there was no correlation between the blood concentrations of glucose and of the keto acids.—F. E. HYTTEN

The Glucose Tolerance Test with Simultaneous Measurement of Blood Sugar and Blood Pyruvic Acid in Diabetic Subjects. M. Moreau, S. Bonfils, R. Deuil, P. M. de Traverse, and G. Hadjissotirion. *Presse méd.* 61: 1379, 1953.

The simultaneous measurement of blood sugar and blood pyruvic acid during the glucose tolerance test was carried out in 25 diabetic and 9 normal subjects. In the normal subjects, blood sugar and blood pyruvic acid evolved in parallel fashion. In 14 of the diabetics, the results were identical: blood pyruvic acid remained stable. On the other hand, 11 of the diabetics had an abnormally high blood pyruvic acid level, apart from any acidosis, although the blood sugar changes were practically identical to those of the preceding group.

This clinical division was reflected chemically: the diabetics with low blood pyruvic acid values were insulin-sensitive. On the other hand, the diabetics

with elevated blood pyruvic acid values were relatively or totally insulin-resistant.—H. GOUNELLE

The elevated levels of blood cholesterol observed in many uncontrolled diabetics have been explained by the finding of increased cholesterol genesis which occurs in the presence of reduced glycolysis. The disposal of the 2-carbon fragments derived from fatty acid oxidation may be hindered by the lack of available oxalacetate; lipogenesis and other biosynthetic processes are limited under these conditions. The mechanisms involved in cholesterol formation are unimpaired and the increased concentrations of acetate precursor lead to a significant rise in its concentration in the blood.

Mechanism of Increased Hepatic Cholesterol-genesis in Diabetes: Its Relation to Carbohydrate Utilization. S. Hotta, R. Hill, and I. L. Chaikoff. *J. Biol. Chem.* 206: 835, 1954.

Normal and alloxan-diabetic rats were fed either a high glucose or a high fructose diet. When the animals were studied to determine the rates of incorporation of C^{14} of acetate-1- C^{14} into cholesterol, the capacity of the liver of the glucose-fed diabetic rat to incorporate C^{14} into cholesterol was more than twice that observed with livers of normal rats fed either the high glucose or the high fructose diet. The rate of cholesterol formation in the liver of diabetic rats was restored to normal by the feeding of the high fructose diet. The difference between the livers of the fructose-fed and glucose-fed diabetic rats was observed as early as 16 hours and as late as 3 weeks after the start of the feeding.

The evidence indicates that the reduction of cholesterol C^{14} recoveries observed in the experiments with the livers of the fructose-fed, diabetic rats is not the result of a change in the C_2 pool size, and it is reasonable to infer that restoration of glycolytic activity in the diabetic liver induced by fructose feeding is responsible for diverting the C_2 fragment from the path of cholesterol synthesis to other metabolic pathways, presumably lipogenesis.—M. K. HORWITT

The Renal Excretion of Inositol in Normal and Diabetic Human Beings. W. H. Daughaday and J. Larnar. *J. Clin. Investigation* 33: 326, 1954.

It has been known for some time that patients with diabetes have an increased amount of inositol in the urine. By the use of microbiologic assay methods, the excretion of inositol in the urine of eleven non-diabetic subjects was compared with that of seven uncontrolled diabetic patients. The increased excretion of inositol in diabetes was confirmed. However, the inosituria of diabetes disappeared after the control of glycosuria.

After the ingestion of 3 g of inositol, there was a much higher increase in the average urinary excretion

in the diabetic group as compared with the controls. Furthermore, following the slow intravenous administration of 20 mg of inositol per kilogram, diabetic subjects excreted three times more in their urine than nondiabetic subjects. Renal clearance studies lead the authors to conclude that a renal tubular mechanism for the reabsorption of inositol exists and that the transport of inositol by the renal tubules is inhibited under high glucose loads. Thus it appears that the increase in inositol in the urine in diabetes can be attributed to an increased clearance produced by glycosuria but not by polyuria.—S. O. WAIFE

Diketogulonic Acid and Diabetes Mellitus. A. W. Marcovich and J. F. Marcovich. *J. Lab. & Clin. Med.* 42: 681, 1953.

Based upon production of diabetes mellitus in possible relation to diketogulonic acid in animals, measurement of this material in the blood of an incompletely defined group of 28 human diabetics and 27 "non-diabetics" was attempted. Diketogulonic acid (or a related chromogen) was found in the blood of all diabetics in contrast to controls. Analytical chemical data with respect to validation of accuracy and precision of the new method employed are meager.—R. TARAIL

The mechanism involved in the interference of isoniazid with carbohydrate metabolism is not clear. In some patients, there is a marked increase in appetite with subsequent increase in food intake and weight gain. This may be a factor in the increase in blood sugar of diabetics treated with this agent unless careful dietary supervision is imposed. The drug has been shown to increase the rate of pyridoxine excretion, which has led to neuritis, but without effect upon carbohydrate metabolism. It would be of interest to know whether this agent acts as an anti-vitamin factor with reference to nicotinic acid in its role in the phosphopyridine nucleotides.

Effect of Isoniazid on Carbohydrate Metabolism in Controls and Diabetics. G. R. W. N. Luntz and S. G. Smith. *Brit. M. J.* 1: 296, 1953.

The oral glucose tolerance test was performed on both diabetic and nondiabetic tuberculous patients. It was shown that the administration of isoniazid produced a temporary elevation of the blood sugar level and impaired the tolerance. This effect was not due to the drug itself, although it is a reducing agent. A disturbance in carbohydrate metabolism is inferred. The fasting blood sugar of 6 diabetics before isoniazid was 255 mg per 100 ml. After 6 days of isoniazid, the fasting blood sugar level was 307 mg per 100 ml.—S. O. WAIFE

The following abstracts present views expressed on some of the special problems encountered in diabetes:

diet, liver disease, cellular glucose, index of severity, and metabolic intermediates. This survey of diabetes closes with a provocative point of view on the pathogenesis of diabetes.

The Problem of the Diet of the Diabetic Child. Effect of a Considerable Increase of Dietary Carbohydrate on Glycosuria and Insulin Requirements. H. Lestadet and A. Senaey. *Presse méd.* 62: 707, 1954.

At the first French summer camp for diabetic children, the authors had the opportunity of studying, in eight children, the effect of a sudden modification of the diet on 24-hour glycosuria levels and on insulin requirements.

No parallelism was observed between the increase of the carbohydrate ration and glycosuria in subjects receiving an adequate amount of insulin. These findings seem to the authors to constitute a supplementary argument in favor of an exclusively insulinic treatment of childhood diabetes, on the condition that rigorous control be exercised and that the daily insulin dosage be adapted to the results of glycosuria determinations carried out every two or three days.—H. GOUNELLE

Diabetes Cured by Laënnec's Cirrhosis. J. Caroli, J. Eteve, and J. Bertrand. *Sem. Hép. Paris* 12: 607, 1953.

The authors report three cases of cirrhosis with ascites which appeared, in the course of their evolution, to bring about the complete cure of diabetes of long standing.

The anti-diabetic effect of Laënnec's cirrhosis might be related to the following experimental data: the hypoglycemia after hepato-pancreatectomy is the same as in the case of simple hepatectomy; secondary hepatectomy, in the dog, causes the disappearance of the diabetes resulting from pancreatectomy.—H. GOUNELLE

Is there an Increase of Cellular Glucose in the Diabetic Subject? H. Lestrade. *Presse méd.* 61: 466, 1953.

It is generally admitted that a high blood sugar level is accompanied by a correspondingly high level of cellular glucose, and that the latter is, to an important extent, responsible for the complications occurring in the diabetic.

The author shows that in the diabetic as well as in the normal subject the space in which glucose is distributed is identical with the extracellular space. It seems, therefore, that there is no free glucose within the muscle cell, and that free glucose is dispersed solely throughout the extracellular environment. These facts contribute a supplementary argument in favor of the concept which regards diabetes not as a disturbance of intracellular carbohydrate

metabolism, but only as a condition in which the passage of glucose into the cell is hampered.—H. GOUNELLE

The Relationship Among Glycosuria, Food Intake, and Body Weight in Alloxan Diabetes. F. M. Sturtevant, L. D. Calvin, and N. E. Fuller. *Metabolism* 3: 262, 1954.

An index of the severity of diabetes has been established which is independent of food intake and body weight, using a multiple regression analysis of the relationships among glycosuria, food intake, and body weight in alloxan diabetes. Removal of the effect of intake and weight reduced the variability in diabetic glycosuria by 88 per cent. Either intake or weight alone accounted for 84 per cent of the variability in glycosuria. An index of severity of diabetes was calculated by dividing the daily glycosuria by the daily food intake. This index is not related to food intake or body weight and indicated that over 50 per cent of the available glucose was excreted in the urine. It would appear that alloxan induces in rats a permanent diabetes of fairly constant severity.—C. R. SHUMAN

Endocrine Influences on Diabetic Index of Alloxanized Rats. F. M. Sturtevant and N. Hansen. *Am. J. Physiol.* 179: 21, 1954.

The diabetic index may be defined as the glucose excretion corrected for variations in food intake. This index is independent of variations in body weight. The test objects in this study were alloxan diabetic rats fed *ad libitum*. The "glycosuria/intake" ratio was reduced by adrenalectomy. However, lethal doses of cortisone or thyroxine increased the ratio. The following were without significant effect: sublethal amounts of cortisone or thyroxine, corticotropin, diethylstilbestrol, cobaltous chloride, or partial thyroparathyroidectomy-thiouracil treatment. The authors believe that the primary disorder in alloxan diabetes is a relative deficiency of insulin compared to the endogenous secretion of adrenal cortex and that these data support such a hypothesis.—M. J. OPPENHEIMER

The Hexose-Monophosphates, the Triose-Monophosphates and Pyruvic Acid—Their Study in the Blood of Normal and Diabetic Subjects. R. Boulou and P. Nepveux. *Le Diabète* 2: 51, 1953.

Carbohydrate metabolism, regarded from the standpoint of the three metabolites studied, behaves in an apparently similar fashion in the healthy subject and in the diabetic subject. Three sets of facts, however, merit attention.

The increase in hexose-monophosphates under the influence of insulin, which is constant in the normal subject, is not observed in the diabetic subject. This difference constitutes a major characteristic of the

dysfunctioning carbohydrate metabolism in diabetes. The triose-phosphates seem to play a regulatory role in the experimental disturbances induced by the authors. Finally, the changes in blood pyruvic acid testify to the predominant role exercised by the processes of oxidation and reduction in carbohydrate metabolism.—H. GOUNELLE

A Concept of Diabetes. W. P. U. Jackson. *Lancet* 2: 625, 1955.

This interesting and somewhat provocative paper examines the natural history of diabetes with particular reference to the effect of childbearing on the so-called prediabetic. A great many personal and borrowed data are used in illustration and it is not possible to condense it adequately for abstract purposes.

Briefly, the conclusions reached are as follows:

Pregnancy is a dangerous stress to the pancreas as evidenced, in part, by the worsening of established diabetes during pregnancy, by the appearance of retinopathy during pregnancy, by the occasional occurrence of hyperglycemia in nondiabetics which disappears postpartum, and by the hypertrophied "pregnancy" pancreas.

Pregnancy is diabetogenic to the fetus; "the abnormal uterine environment of the prediabetic may produce a baby which is stillborn, gigantic and cushingoid, or a child who grows too tall, has an abnormal vascular system and develops diabetes."

"We do not know the cause of diabetes, nor do we understand its very real relation to growth and size; but apparently diabetes in the latent form ('prediabetes') remains with the victim years or decades before he or she becomes overtly diabetic." During this time pregnancy, corticotrophin therapy, acquisition of Cushing's syndrome or of acromegaly, a staphylococcal infection, or overeating, may uncover the individual already predisposed to diabetes. The previously adequate compensating pancreas cannot stand the additional stress completely, and evidence of the latent diabetic state is brought to the surface, divulging its menacing presence by embryopathies, or changes in carbohydrate tolerance. Hence it is wrong to talk of diabetes only when glycosuria and hypercalcemia are present. It is a disorder which goes back much further than that—even into the womb.—F. E. HYTEN

CARBOHYDRATE METABOLISM

With mass screening of the population for evidence of diabetes mellitus, it becomes important to determine the influence of the previous diet upon glucose tolerance. There has been adequate evidence that high fat feedings or starvation will impair glucose tolerance. It has been recommended that a 250- to 300-gram carbohydrate diet be fed for a period of 3 days prior to the performance of the glucose tolerance

test. However, the report below reveals data that lend further weight to the practicality of mass screening of the population.

The Effect of the Previous Diet on Glucose Tolerance Tests. E. M. Irving and I. Wang. *Glasgow M. J.* 35: 275, 1954.

It has been suggested that the glucose tolerance test may give an abnormal result in a normal person on a low carbohydrate diet; a preliminary diet containing 300 grams of carbohydrate daily has been recommended, but many persons find this excess nauseating.

Nine medical students and three laboratory staff members, 7 males and 5 females aged 19 to 25 years, were subjects in an investigation where 9 of them were given 100 g of carbohydrate daily for 4 days before the first glucose tolerance test and then 300 g daily for 4 days before a second test. In the other three subjects, the procedure was reversed.

Full details of the investigations are recorded. Briefly, the fasting blood sugar was not significantly different on the two types of diet. In no case did the glucose tolerance test show a diabetic curve, although three subjects on the low carbohydrate diet showed an oxyhyperglycemic ("lag") curve. Every subject lost weight on the low carbohydrate diet, and it is concluded that since this did not cause any significant alteration in the result of the test, anyone who is maintaining his weight on a normal diet, requires no special preparation for the test.—F. E. HYTEN

Many factors affect the utilization of carbohydrate. Among these are the thyroid gland, previous adaptation to high fat feeding, and the simultaneous ingestion of other nutrients. These subjects are discussed in recent reports.

Effect of Thyroidectomy and Food Intake on Oral and Intravenous Glucose Tolerances in Rats. R. O. Scow and J. Cornfield. *Am. J. Physiol.* 179: 39, 1954.

Thyroidectomized rats were subjected to forced feeding. Marked obesity and increase in body size were the results. Oral and intravenous glucose tolerance curves were not changed by alterations in food intake or body size in normal controls or in rats deprived of their thyroid glands. When the intravenous route was used, glucose tolerance was impaired by thyroidectomy. In the case of the oral route, the hyperglycemia of thyroidectomized rats was 50 per cent above that observed in normal controls. In intravenous tests, glucose was removed from blood much more slowly during the first 20 minutes than during the following 100 minutes. It is tentatively suggested that this last observation may be due to a 20-minute delay in the onset of urinary excretion.—M. J. OPPENHEIMER

Ketogenesis in Rats on High Carbohydrate and High Fat Diets. H. M. Tepperman and J. Tepperman. *Am. J. Physiol.* 180: 511, 1955.

Several groups of rats were adapted to synthetic isocaloric diets either high in carbohydrate or high in fat. While subsisting on these diets the animals on the high fat intake had a higher blood ketone concentration. On the other hand, when a 24-hour fast was imposed, those which had previously been on a high carbohydrate diet had a higher blood ketone level. When liver slices were examined from animals previously fed a high fat diet they were observed to produce more ketone bodies than slices from the carbohydrate controls. On the other hand, after fasting 24 hours (following a high fat diet) the slices make much less ketone bodies than controls on carbohydrate. The octanoate oxidizing capacity was found to be unchanged by a high fat diet. Washed liver particles from fat-fed livers oxidize octanoate poorly, but there is no change in their ability to oxidize ketoglutarate. The Krebs cycle intermediates may be deficient when octanoate cannot be oxidized in fat-fed livers. It was shown that fortified homogenates from fat-fed livers produce more ketone bodies and show less oxygen use and ketone production when octanoate is added than do similar homogenates from livers of carbohydrate-fed rats.—M. J. OPPENHEIMER

Effects of Mixed Foods on the Blood Levels of Glucose, Amino Acids and Chylomicrons. H. Singer, J. Sporn, A. Bridgwater, and H. Necheles. *J. Appl. Physiol.* 7: 443, 1955.

Blood glucose curves were studied when glucose alone was fed. These curves were compared to those obtained when glucose was fed in combination with gelatin, or with cream, or with both. The curve obtained when glucose was fed in any combination was depressed below control values. In addition, when gelatin was fed with glucose, with cream, or with both, the blood amino acids curves observed were depressed below those obtained when gelatin was fed alone. Plasma chylomicron curves were studied when fat alone was fed. These were unchanged when fat was fed with gelatin, with glucose, or with both.—M. J. OPPENHEIMER

The utilization of glucose by liver slices has been shown to be delayed, no appreciable effect being observed within the first 6 hours. In contrast, there is immediate uptake and utilization of glucose by muscle tissue. The more rapid removal of glucose administered orally over that of intravenous glucose is difficult to explain except through the formation of hexose phosphate within the liver cells. Apparently such phosphorylated compounds are not rapidly utilized or converted to glycogen. Evidence of possible roles for atropine and heparin is indicated.

Quantitative Relations Between the Oral and Intravenous Glucose Tolerance Curves. R. O. Scow and J. Cornfield. *Am. J. Physiol.* 179: 435, 1954.

The oral glucose tolerance curve is the resultant of the balance between overall glucose removal rate and that of intestinal absorption. An expression is derived for this which demonstrates that the removal rate for oral glucose is roughly three times that for intravenous glucose. A higher liver uptake of glucose in oral administration may explain this observation. Glycogenesis in the liver does not account for it.—M. J. OPPENHEIMER

Atropine and Glucose Metabolism in Goats. P. F. Robinson and C. G. Wilber. *Am. J. Physiol.* 181: 481, 1955.

In these experiments the normal fasting blood sugar was about 80 mg per 100 ml. Glucose tolerance curves were observed to reach a maximum of 196 mg per 100 ml. At the end of two hours the blood sugar had returned to control values. Prolonged fasting up to 16 days produced changes in the glucose tolerance curves. The maximum was now 140 per cent of controls in 15 minutes. The elevation was maintained for a long time, since the values were increased up to 130 per cent over those of controls three hours later. When goats were given atropine, similar results were obtained. In this latter case, the mean blood glucose values observed were more than twice those in controls. After three hours the blood sugar was still more than 160 per cent above that in the control series. No definite explanation is offered. The possibility of a direct action of atropine on the sympathetic nervous system is suggested; this would be similar to the action of epinephrine on the same system.—M. J. OPPENHEIMER

Effects of Heparin on Carbohydrate Metabolism in the Rabbit. B. D. Bond and J. J. Spitzer. *Am. J. Physiol.* 180: 575, 1955.

In fasting rabbits heparin increases the blood glucose level. This effect may be blocked by Priscoline. On the other hand, heparin does not affect epinephrine hyperglycemia significantly. The effect of the hyperglycemic factor of the pancreas (glucagon) is likewise unchanged by heparin. Furthermore hypoglycemia due to insulin is reduced by heparin. The authors reach the conclusion that heparin causes the release of epinephrine in the rabbit.—M. J. OPPENHEIMER

Fluoroacetate exerts an inhibiting effect upon tissue metabolism by influencing the oxidative reactions of the tricarboxylic acid cycle. This metabolic block permits research into the depths of intermediate metabolism.

Carbohydrate and Ketone Body Metabolism in the Sodium Fluoroacetate-Poisoned Rat. "SFA Diabetes." F. L. Engel, K. Hewson, and B. T. Cole. *Am. J. Physiol.* 179: 325, 1954.

Sodium fluoroacetate (SFA) was injected intraperitoneally. Twenty-four hours later hyperglycemia and hyperketonemia were observed. SFA poisoning prolonged the duration and degree of octanoate sodium ketonemia which was considered to be due to increased production and decreased ketone utilization. SFA poisoning did not affect ketonemia due to fat emulsions, whatever the route of administration. Glycerol and glycerol monoacetate were more effective than glucose in decreasing ketosis by elevating blood sugar levels. Cortisone opposed ketosis without affecting blood sugar levels. The authors consider that hyperglycemia and ketonemia of CFA poisoning represents diabetes mellitus secondary to general metabolic action on tissues or action of beta cells of the pancreas influencing insulin production.—M. J. OPPENHEIMER

Effect of Fluoroacetate on Glucose Metabolism in vivo. W. B. Elliott and A. H. Phillips, Jr. *Arch. Biochem. & Biophys.* 49: 389, 1954.

Since the demonstration of accumulation of citrate in the tissues of fluoroacetate-poisoned animals, several workers have utilized fluoroacetate to demonstrate the importance of the tricarboxylic acid cycle in the tissues of various animals and organisms by analyzing the tissues for the accumulated citrate. It seemed probable that the presence of a partial or complete block in the tricarboxylic acid cycle in various tissues would interfere with the removal of products of glycolysis and lead to a disruption of glucose metabolism.

In an effort to evaluate the effect of fluoroacetate on glucose metabolism *in vivo*, single and daily injections of sublethal amounts of fluoroacetate were made and the effect on blood sugar levels was observed in the albino rat. Initial injections of fluoroacetate produced a marked rise in blood glucose and subsequent injections caused similar rises, indicating some accommodation to fluoroacetate by the albino rat. Repeated injections of sublethal doses led to prolonged elevations of blood glucose. There were some indications of rat strain differences in the quantitative effect of fluoroacetate on glucose metabolism.—M. K. HORWITT

The occurrence of insulin reactions in the presence of normal blood sugars has not been satisfactorily explained. It is now believed that the rate of change in the glucose concentration is more significant than the actual values observed. However, there are still many conditioning factors involved which require further study.

Clinical versus Laboratory Hypoglycemia. M. Fabrykant. *Metabolism* 4: 153, 1955.

The arteriovenous (A-V) glucose differences were determined by obtaining capillary and venous blood glucose determinations during oral glucose tolerance tests. Of the 76 patients tested, 13 suffered from spontaneous hypoglycemia and the remainder from a variety of clinical conditions in which this abnormality was suspected. Clinical manifestations observed during the tests revealed weakness and hunger to be the most common hypoglycemic symptoms. Subnormal blood glucose values were registered in spontaneous hypoglycemia, as well as in conditions not accompanied by such manifestations. The onset of symptoms was found in most instances to precede the fall in blood glucose to its nadir and occurred when the glucose levels were normal or even moderately elevated. In seven instances, subnormal values were not attended by hypoglycemic symptoms. The discrepancies between clinical and laboratory features of hypoglycemia are explained on the basis of metabolic and functional disturbances in the central nervous system resulting from declining blood glucose values, rather than ascribed to the actual level itself. Inversion of the A-V glucose difference was noted in most tests at the blood glucose nadir. No relationship was observed between the clinical symptoms and the A-V glucose alterations. The influence of the psychological make-up of the individual upon the hypoglycemic manifestations is described.—C. R. SHUMAN

An important species difference in the influence of glucose utilization for formation of energy by the myocardium has been demonstrated. This is a significant finding in the evaluation of cardiac metabolism in the laboratory.

Species Differences in the Utilization of Glucose for Contractile Force by Isolated Perfused Hearts. S. Garb, M. Penna, and A. Scriabine. *Am. J. Physiol.* 180: 103, 1955.

The test objects were isolated perfused mammalian hearts. Species differences were marked when the action of glucose on the force of cardiac contraction was studied. In cases where the substrate was depleted, the rat's heart was observed to have a 50 per cent increase in the force of contraction when glucose was added. Responses from hearts of other species were less. In the case of the guinea pig, the increase was 12 per cent, while in the rabbit it was 8 per cent, but only 4 per cent in the cat.—M. J. OPPENHEIMER

Relationship of Temperature to the Utilization of Glucose for Contractile Force by Cat Heart Muscle. S. Garb and A. Scriabine. *Am. J. Physiol.* 180: 101, 1955.

In these experiments the contractile force of isolated cat papillary muscles was tested. When the glucose concentration was 200 mg per cent at 37° C., there was a small increase in contractile force. However, when these same concentrations were observed at a temperature ten degrees lower, the effects were a much more marked increase in contractile force. These results emphasize the fact that temperature must be considered when the effects of various substrates are studied for their action on the isolated mammalian myocardium.—M. J. OPPENHEIMER

It has been shown that the concentrations of several of the digestive enzymes is increased in the presence of a high intraluminal concentration of their respective substrates. Presumably this applied equally well to the enzymes operating in the processes of absorption.

The Role of Alkaline Phosphatase in Intestinal Absorption. II. The Effects of Various Carbohydrates on Levels of the Enzyme on Intestinal Mucosa. J. Tuba and N. Dickie. *Canad. J. Biochem. & Physiol.* 32: 621, 1954.

Adult male albino rats were deprived of food for five days. Groups were then given powdered cellulose, alone or with one of seven other carbohydrates. Six hours after being given the food, the rats were killed and a piece of intestine from each was tested for alkaline phosphatase. The activity of the enzyme was increased significantly by the ingestion of glucose, galactose, fructose, and mannose, but not by cellulose, arabinose, xylose, or sucrose. Sucrose can be split by fasted animals and it is suggested that the lack of response to sucrose, in contrast to glucose and fructose severally, may be because the two sugars are present together in equal amounts.

It is concluded that "alkaline phosphatase may participate in the enzymatic mechanisms associated with the absorption of sugars from the intestine."—F. E. HYTTEN

The high levels of blood glucose seen in diabetes mellitus which may persist for long periods will tend to increase the osmolarity of extracellular fluids and alter the water:solids ratio of various tissues, such as the lens of the eye. It is likely that such osmotic changes will alter the lens protein, leading to cataract formation in certain instances. In addition, the lens may be damaged by changes in the metabolic abnormalities coincident with sustained hyperhexosemia. These problems are obviously of clinical importance.

Relation between Blood Sugar Level and the Optical Properties of the Lens of the Human Eye. D. W. Vere and D. Verel. *Clin. Sci.* 14: 183, 1955.

Although this paper is largely concerned with ophthalmological technicalities, it presents new data on

the subject of the common, transient dimness of vision which effects diabetics.

It is shown that an increasing blood sugar level is associated with a dimming of the red reflex of the eye in both normal and diabetic patients. The change appears to be due to "a reversible opacification of the front of the lens of the eye."

The authors suggest that these lens changes may be at least partly responsible for the transient dimness of vision suffered by diabetic subjects when hyperglycemic, and may be related to the formation of diabetic cataracts.—F. E. HYTTEN

Hyperglycemia and Galactose Cataracts. J. W. Patterson. *Am. J. Physiol.* 177: 541, 1954.

When increasing amounts of galactose were added to the diet of rats the blood sugar, urine sugar, urine volume, water and food intake all increased in a parallel manner. It was found that galactose intake and weight gain are inversely proportional. Cataracts form more quickly when galactose blood levels are high; in fact, galactose is four times as effective as glucose in the production of cataracts. Lowering of the blood sugar with phlorizin delays the development of cataracts by as much as 35 per cent.—M. J. OPPENHEIMER

INSULIN AS A NUTRITIONAL FACTOR

In the total body economy there are probably few if any more important substances than the hormone of the beta cells of the pancreas, insulin. It is essential for the formation of energy within most of the tissue cells, and from this energy the tissues derive their ability to perform work of various specialized types. The fabrication of protein from amino acids and the deposition of fat stores depend upon its presence in the body. Although virtually all of the effects attributable to insulin can be accounted for on the basis of its action in converting extracellular glucose to intracellular glucose-6-phosphate, there are other observations concerning its physiological and biochemical influences which are admirably recounted below. In addition, a recent report notes an association between plasma insulin levels and the clinical type of diabetes.

Current Views on the Mechanism of Insulin Action. W. C. Stadie. *Am. J. Med.* 19: 257, 1955.

The background of our present understanding of diabetes, the catalytic action of enzyme systems and the general aspects of intermediary metabolism are presented in the introduction of this excellent report. The sites of insulin action which are currently under discussion are: (1) increase in cell permeability or transfer of glucose across cell barriers to enzymatic sites; (2) acceleration of the hexokinase

reaction; (3) increase in high energy phosphate formation; and (4) effect on oxidative reactions of the Krebs cycle. Each of these mechanisms is discussed together with the experimental evidence upon which the concepts are based.

The difficulty of demonstrating direct insulin action on the liver is evidenced by the conflicting evidence found in the literature. The hepatectomized animal requires far less glucose to maintain a constant blood sugar than does the animal with an intact liver. The assumption that the extra glucose in the intact animal goes into hepatic glycogen has been challenged by Levine *et al.* The latter workers have shown that peripheral glucose uptake is decreased following hepatectomy. This suggests that a "humoral" factor from the liver stimulates glucose utilization by muscles. Renold, Hastings, *et al.* have shown that insulin produces an immediate response in muscle but that hepatic carbohydrate metabolism shows only a minimal effect after 6 hours as measured by glucose uptake, glycogen deposition, or pyruvate and CO₂ production. In the absence of insulin, the liver is incapable of incorporating labeled glucose into fatty acids. Prolonged treatment with insulin is necessary to restore fatty acid synthesis. The failure of lipogenesis by the diabetic liver is not a primary defect but is secondary to loss of ability to utilize glucose. The same explanation pertains to disturbances in protein metabolism in insulin deficiency. This thorough review closes with a discussion of the binding effect between insulin and muscle tissue.—C. R. SHUMAN

Plasma-Insulin Activity in Diabetes Mellitus. Measured by the Rat Diaphragm Technique. J. Vallance-Owen, B. Hurlock, and N. W. Please. *Lancet* 2: 583, 1955.

Plasma-insulin activity was studied in the two broad clinical types of diabetes mellitus.

In the obese group, who do not require insulin injections, insulin activity was found. The activity in the fasting state was greater than in normal fasting subjects. When a known amount of insulin was added to the plasma from these patients *in vitro* it was satisfactorily recovered.

In uncontrolled but nonketotic diabetics who require insulin, no plasma-insulin activity was found, and when insulin was added to the plasma of these patients *in vitro* it was not recovered, its activity being apparently inhibited. When the patients in this group were controlled, however, plasma insulin activity was found.

The findings suggest that many diabetics require insulin to overcome an inhibitor circulating in the plasma, thus explaining why diabetics often require more insulin than depancreatized human subjects. There is some speculation on the nature of this inhibition.—F. E. HYTTEN

Observations such as the following strengthen the view that insulin acts to increase the rate of movement of certain hexoses into the cell. According to this theory, phosphorylation of the hexose by specific kinases within the cell occurs spontaneously as its concentration increases.

Metabolism of Mannose by the Extrahepatic Tissues. D. R. Drury and A. N. Wick. *Am. J. Physiol.* 177: 535, 1954.

Mannose is able to pass from the extracellular to the intracellular compartments of extrahepatic tissues. In this regard it resembles glucose and galactose. This transfer is accelerated by insulin. Glucose and mannose compete in entering cells under insulin acceleration. Mannose, in the eviscerated non-nephrectomized rabbit, is excreted largely by the kidney when injected into the blood stream. Under the influence of insulin, extrahepatic tissues oxidize large amounts of mannose to CO_2 .—M. J. OPPENHEIMER

Amelioration of pre-existing diabetes following pituitary necrosis has been reported in 13 instances in the medical literature; hypophysectomy is currently under study as a method for improving the status of the severe diabetic with vascular complications involving the retina and kidneys. Apparently there is a decreased rate of insulin degradation following hypophysectomy. The administration of thyroxine, on the other hand, increased insulin inactivation, resulting in a deterioration of the diabetic status.

Pituitary and Adrenal Influences on Insulin- I^{125} Degradation. N. J. Elgee and R. H. Williams. *Am. J. Physiol.* 180: 9, 1955.

After hypophysectomy, degradation of insulin- I^{125} was markedly diminished. In part, this may explain increased insulin sensitivity in hypophysectomized animals. On the other hand, degradation of insulin- I^{125} was unchanged after adrenalectomy. Hydrocortisone and growth hormone also had no action. Changes in carbohydrate metabolism seem to be unrelated to insulin degradation.—M. J. OPPENHEIMER

Effects of Thyroid Function on Insulin- I^{125} Degradation. N. J. Elgee and R. H. Williams. *Am. J. Physiol.* 180: 13, 1955.

The metabolism of I^{125} -labeled insulin probably is the same as that of unlabeled insulin. If this is so, the increased degradation of insulin- I^{125} produced by thyroxine and tri-iodothyronine may indicate an accelerated metabolism due to these substances. It is also possible that insulin is inactivated without having been "used" or having produced a physiological effect. Thyroid hormone might also speed up this sort of mechanism. In contrast, thyroidectomy

decreased insulin degradation. In this case the metabolism was decreased. It is known that the insulin requirement rises in hyperthyroidism. This could result from increased insulin degradation, a relative insulin insufficiency, and hence, an increased requirement.—M. J. OPPENHEIMER

The following observation raises the question of a trophic hormone arising from the pituitary to influence the rate of insulin genesis. Such a trophic factor has never been demonstrated. Interference with the peripheral action of insulin may result in the final exhaustion of the beta cells which have reacted to anti-insulin factors by an increased rate of insulin formation.

Influence of Prolactin on Blood Sugar in Normal and Depancreatized Dogs. P. P. Foa, G. Galansino, H. R. Weinstein, and A. M. Magill. *Am. J. Physiol.* 180: 313, 1955.

Initial intravenous doses of prolactin lower blood sugar. There occurs at the same time a marked degeneration of beta cells in the islets of Langerhans. Nevertheless, subsequent intravenous injections of prolactin produce partial recovery of beta granulations, accompanied by hyperglycemia. However, if the dogs are depancreatized, then the very first dose of prolactin is observed to produce hyperglycemia. The possibility is suggested that first doses of prolactin release preformed insulin but that later doses exhaust the beta cells. This latter state, then, is associated with hyperglycemia. Hormones of pituitary, adrenal, or pancreas which are "anti-insulin" in action cannot entirely account for the hyperglycemia, because it is still present when these glands have been extirpated.—M. J. OPPENHEIMER

ITEMS OF GENERAL INTEREST

Recent Advances in Nutrition of Public Health Significance. N. Jolliffe. *Metabolism* 4: 119, 1955.

The rapidly expanding world population is introducing serious problems in maintaining food supplies. Despite an increasing production of animal feeds, an overall shortage of animal protein, which depends ultimately upon cereal grains, may become a problem in this country as it is elsewhere in the world. It is emphasized that our consumption of "empty calories" has increased progressively until at the present time a total of 32.3 per cent of our intake is in this form. "Empty calories" are those sources of body energy which are nearly devoid of protein, minerals, or essential vitamins and are composed largely of sugars, syrups, and cooking fats. It is suggested that the consumption of empty calories could be halved and greater use be made of non-caloric sweeteners, so that sugars and fats will be provided

in foods which supply the essential nutritional factors (fruits, vegetables, grains, milk, cheese, eggs, etc.).

Amino acid fortification of basic cereal grains is proposed as a method of extending the world's supply of high-grade protein. This is in keeping with the concept that the correct proportion of amino acid is more important than total protein intake. The "amino-gram" for whole wheat protein reveals a deficiency of lysine which becomes a limiting factor in the value of this food as a protein source. Approximate supplementation of all the cereal proteins with certain amino acids will produce biologically acceptable forms of protein food for growth and repair of tissues.

The growth-promoting effects of vitamin B₁₂ and antibiotics have been studied in both animals and humans. In several groups of children, vitamin B₁₂ has been shown to produce weight gain where nutritional factors have been responsible for growth retardation. Preliminary observations with antibiotics have shown similar results.—C. R. SHUMAN

Effect of Prolonged Antibiotic Administration on the Weight of Healthy Young Males. T. H. Haight and W. E. Pierce. *J. Nutrition* 56: 151, 1955.

That antibiotic prophylaxis during periods of epidemic streptococcal infections markedly reduces the number of infections, complications, and sequelae in the population has been clearly demonstrated. Little information is available, however, on other less specific effects of such widespread antibiotic administration to large groups of people. In the course of a study on the effects of antibiotic prophylaxis on the immune response in humans, it was recognized that there was a unique opportunity to observe the influence of prolonged antibiotic administration on the weight behavior of healthy young males.

Six companies of Navy recruits were distributed at random into one of three "treatment" groups, and all subjects received once daily for seven weeks one of the following identical-appearing preparations: (1) Aureomycin, 250 mg; (2) oral, buffered, procaine penicillin, 100,000 units; or (3) a placebo (calcium carbonate). Observations on the nude weight and height were made initially and again 4 and 7 weeks later. The individual and group weight changes were then calculated, both in pounds and in relative body weight (actual weight expressed as a per cent of the standard weight for age and height). Final data were available on 310 men. Both the initial changes after 4 weeks and the total changes after 7 weeks revealed a distinct difference between the placebo group and the antibiotic groups. The Aureomycin and penicillin groups were not significantly different. This difference in weight gain between the placebo group (2.7 pounds) and the antibiotic groups (average 4.5 pounds) was reflected in roughly an equal degree of difference in relative body

weight gain, and this would be expected due to chance alone less than 5 per cent of the time.

A similar study was conducted, but without administering any capsules, to determine normal group-to-group variation in this population. No significant differences were encountered in this simulated experiment. These studies were exploratory and suggest further avenues of approach in evaluating the specific nutritional effects of antibiotics in humans.—B. SURE

Observations on the Use of Antibiotic-Vitamin Combinations. K. J. Dumas, M. Carlozzi, and W. A. Wright. *Antibiotic Med.* 1: 296, 1955.

In a study on healthy, normal adults, 12 subjects received 500 mg of an oral suspension of a tetracycline-vitamin combination incorporating the daily vitamin dosage recommended by the National Research Council's Committee on Therapeutic Nutrition for periods of stress (thiamine, 10 mg; riboflavin, 10 mg; niacinamide, 100 mg; calcium pantothenate, 20 mg; pyridoxine, 2 mg; folic acid, 1.5 mg; vitamin B₁₂, 4 µg; ascorbic acid, 300 mg; vitamin K, 2 mg). Blood samples were taken before administration and at hours 2, 4, 6, and 8 afterwards. Fourteen subjects received the same amount of tetracycline-vitamin combination in capsule form, with blood samples obtained as above. Sixteen persons received similar capsules four times a day for three days; blood samples were withdrawn from these subjects before administration of the first capsule; at hours 2, 4, and 6 after the first; and once a day thereafter.

Blood levels of tetracycline obtained with the antibiotic-vitamin combination were comparable to those achieved with tetracycline alone. It would appear that the addition of vitamins in amounts meeting the NRC recommendations does not interfere with the attainment of antibiotic levels adequate for most infections.—C.-J. HOWELL

Nutrition as a Military Problem. H. R. Sandstead and E. M. Parrott. *Military Med.* 117: 54, 1955.

This interesting paper is a review of nutritional problems with which technical and military advisers will be concerned in those Far Eastern countries receiving assistance from the United States. Based on experience in Western Europe, it appears that the impulse to give large quantities of food to starving individuals should be resisted. The most successful therapy in advanced malnutrition consists in providing liquid and soft foods such as milk, eggs, and cooked cereals not exceeding 1500 calories a day for the first few days. The use of oral or parenteral hydrolysates of amino acids and plasma and blood transfusions were seldom indicated. Refeeding should start slowly and proceed with caution.

In the Far East, factors which determine nutritional requirements include the chronically poor nutritional state of the population, the intensity of parasitic infestation, climate, and large energy ex-

penditure. In addition the dietary habits of these people are influenced by centuries-old social and religious customs, while the source, type, and availability of food are determined by Government regulation.

Relatively little factual information is available for this area, in contrast to that for Europe.—S. O. WAIFE

Food Intake of Greek Farm Families. C. Miller and T. Kaumvakali. *J. Am. Dietet. A.* 31: 3, 1955.

This study was undertaken to obtain information on the amount and kinds of food generally eaten by farm families in Greece, so that home agents in the extension program could give practical suggestions. One-week food inventory records were obtained in early June, 1953, from 133 families from more than 100 villages in Rhodes and on the mainland of Greece. This sampling represented 711 individuals: 388 adults, 165 adolescents (10 to 20 years of age), 158 children, and 2 babies under one year. These records were supplemented with estimates of consumption patterns of seasonal foods secured from 548 additional families.

Nutrient content of the diets were calculated and compared as family allowances with the 1953 National Research Council recommended allowances. The number of families receiving 0-100 per cent of the allowances grouped in intervals of ten, e.g., 1-9 per cent, 10-19 per cent, etc., are shown in tabular form. Food records from the 548 families appear as percentage of families receiving 1-21 servings weekly per person of each of the "basic seven" groups.

By comparison with the N.R.C. allowances, high incidences of shortages were reported for calcium, vitamin A, riboflavin, and ascorbic acid.

A discussion of foods which customarily provided important nutrients is of interest. Raw cabbage and tomatoes were responsible for much of the estimated vitamin C. Strawberries, mulberries, melons, green peppers, and raw greens augmented the intakes seasonally. Families who obtained sufficient vitamin A ate large servings of raw greens. Yellow vegetables were used infrequently. Only one family ate liver during the week recorded. Increased production of milk and/or cheese is recommended in order that families meet calcium allowances. Milk is consumed principally as yoghurt and cheese. The authors did not consider the contribution of water, beer, and bones of small fish in making their dietary assay for calcium.

Whole wheat flour provided most of the protein, iron, thiamine, niacin and calories. Daily consumption of 1½ lb of bread by an adult was not unusual. Fats, rice, and macaroni—but little sugar—supplied additional calories.

Production and preservation of meat was considered by the authors to constitute the most serious food problem. The records showed that half of the families obtained enough animal protein to supply

one-third of the allowance. It was believed, however, that the quantity of whole wheat consumed would provide all the essential amino acids needed for maintenance and possibly growth, and that dry legumes, nuts, and rice which are consumed in quantity the year round would increase the biologic value of the wheat proteins.

The authors concluded from their survey that undernourishment was not widespread at the time of their study. Though the variety of foods in the weekly records was very limited, a very small number of families received less than 70 per cent of allowances for most nutrients. It was further stated that some malnourishment may exist when families use corn as the chief cereal and few fresh vegetables, but the country produces enough wheat and rice for its own use, and two gardens a year are possible in most areas; so the major problem would seem to be "better utilization of existing and potential supplies rather than gross insufficiency in any one group."—J. M. SMITH

Manifest Anxiety and Food Aversions. W. Smith, E. K. Powell, and S. Ross. *J. Abnorm. & Social Psychol.* 50: 101, 1955.

Individual preference in foodstuffs is the psychologic basis for an enormous segment of the food and advertising industries. Recently, a study was made to test the hypothesis that a high frequency of food aversions was related to a high level of anxiety.

Three hundred and eighteen college students at Bucknell University and 107 junior and senior high school students in Pennsylvania were given a checklist of 29 foods which frequently are disliked. Psychologic tests for anxiety were also administered.

Interesting differences between males and females in their selection of foods which they refused to eat were uncovered. Among males, the most "unpopular" were brains (49%), buttermilk (42%), kidneys (35%), liver (22.5%), cottage cheese (21%), mushrooms (19%), mush (16.9%), chili (14.8%), and beer (14.8%).

Among females, the order was: brains (67.6%), kidneys (58%), buttermilk (57%), mush (29.5%), beer (24%), liver (24%), mushrooms (23%), cottage cheese (16%), and potato soup (15%).

Ninety-seven per cent of females disliked one or more foods, while 85 per cent of males disliked one or more—a statistically significant difference. In both high school and college groups, females had higher anxiety scores and a higher food aversion frequency. Statistical analysis also reveals that high anxiety scores were correlated with frequent food dislikes for both groups and both sexes.

The student group that reported regular church attendance had less food aversion than nonattenders. As the authors point out, probably a very small proportion of the subjects had direct experience with each food listed; this would be especially true for brains and kidneys. Undoubtedly cultural factors as

well as symbolism of and identification with internal organs are involved here.

While further studies are clearly indicated, the correlation between anxiety and food aversion is an interesting and important clinical matter.—S. O. WAIFE

Nutrition and Fluid and Electrolyte Balance during Treatment of Tetanus. G. Wilson and A. D. Care. *Lancet* 1: 1303, 1955.

A boy of 15 with severe tetanus was kept unconscious for two weeks by continuous administration of nitrous oxide, and convulsions were controlled by continuous intravenous infusion of suxamethonium chloride.

The nutrition of the boy during this period of unconsciousness is described in detail: 1500 calories daily were supplied in about 900 ml of a concentrated gruel containing milk and egg, and additional glucose and salts were supplied intravenously. Details of mineral balances are shown; there were no serious deviations from normal in the blood analyses.

Although the calories supplied were considered to be more than adequate, the boy was nevertheless thought to have lost about 14 pounds body weight during his illness, possibly because he was in negative nitrogen balance.—F. E. HYTTEN

Residual Neuropathological Changes in Canadians Held Prisoners of War by the Japanese. N. Fisher. *Canad. Serv. M. J.* 11: 157, 1955.

In this interesting paper are presented the neuropathologic changes found in 11 ex-prisoners-of-war who, while prisoners at Hong Kong, developed neurological manifestations of nutritional deficiency. These men survived from four to seven years and died of unrelated diseases.

Demyelination of the posterior columns of the spinal cord was found in seven; degeneration of the papillo-macular bundle was found in four.

The term Strachan's disease (based on a report in 1897) is suggested for the relatively clearly defined nutritional neuropathy and associated mucocutaneous changes exhibited by prisoners-of-war in the Far East. Clinical features include "burning feet," numbness, and paresthesias of the feet, hands, and face, sensory ataxia, visual failure, hyporeflexia, and occasionally spasticity.

There is evidence that thiamine plays a subsidiary role, if any, in Strachan's disease, and it would seem that riboflavin, pyridoxine, and pantothenic acid are the known possible responsible agents. It is also conceivable that some as yet unrecognized constituent of vitamin B complex may prove to be important. Unknown factors are also of crucial significance, because different soldiers on approximately the same diet will respond differently. Moreover, Chinese natives eating the same diet as Canadian soldiers did not develop manifestations of deficiency.—S. O. WAIFE

The Use of Beer in the Low Salt Diet with Special Reference to Renal Disease. E. Olmstead, J. E. Cassidy, and F. D. Murphy. *Am. J. Med. Sc.* 230: 49, 1955.

Beer provides a high caloric and low sodium content which stimulated interest in its use in the low salt diet for patients with renal disease, with particular reference to its effect upon the cardiovascular renal system. The patients under observation on calculated diets with and without beer included those with chronic glomerulonephritis, Kimmelstiel-Wilson's disease, and malignant hypertension. The fluid intake was restricted to 2000 cc daily. The nutritional content of beer (1150 cc) is given as 480 calories, 3.20 g protein, 50 g carbohydrate, 40 g alcohol, and negligible amounts of sodium. The beer-supplemented diet was well tolerated and was regarded as more palatable than the regular hospital low sodium diet. There was no clinical or laboratory evidence of increased deterioration in the renal process. The added beer did not provide clinical improvement. One patient receiving the beer-supplemented diet for one year showed no untoward effect from this regimen.—C. R. SHUMAN

Lysine Deficiency and Dental Structure. L. A. Bavetta and S. Bernick. *J. Am. Dent. A.* 50: 427, 1955.

Dental structures were examined in rats which were on a lysine-deficient diet for periods of from 3 to 11 weeks. There was a general retardation of growth. Degenerative changes were seen in the long bones and consisted of beginning osteoporosis and epiphyseal alterations. Repletion of lysine led to increased growth and restoration of chondrogenic activity at an accelerated rate.

Similar changes, i.e., retarded chondrogenesis, degeneration, and failure of calcification (osteogenesis) were also found in alveolar bone and the mandibular condyle. Dentin deposited during the deficiency period appeared to be hypocalcified. The failure to calcify in these experiments appears to be largely the result of inadequate synthesis of matrix.—S. O. WAIFE

Influence of Dietary Flavonoids on Frostbite in the Rat. F. A. Fuhrman. *Am. J. Physiol.* 181: 123, 1955.

Injury was produced by immersion of the foot at -22°C . for 10 seconds after freezing, or at -25°C . for 15 or 30 seconds after freezing. The extent of tissue loss was less in those animals on a diet supplemented with flavonoids. The supplements were hesperidin methyl chalcone or calcium flavonate glycoside. More protection was provided if the injury was not severe. Epinephrine effects were tested on the mesoappendix of the rat. The blood vessels of this test object had a lower threshold to epinephrine in those rats which had been maintained on the flavonoid-supplemented diets.—M. J. OPPENHEIMER

